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THE STRUCTURE AND INNERVATION OF THE CONDUCTIVE SYSTEM OF THE HEART OF THE DOG AND RHESUS MONKEY, AS SEEN WITH A SILVER IMPREGNATION TECHNIQUE

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THE present article is based on studies of serial sections of the heart impregnated with the Cajal silver nitrate technique. Since the presence of a differentiated conductive system in the dog has been questioned recently,[1] most of the work was carried out in this animal; the monkey was used chiefly for comparison and because it is more closely related to man. A correlation of some physiologic phenomena with the anatomic observations will be attempted in the discussion.

I. MATERIAL AND TECHNIQUE

The dog material consisted of the hearts of four puppies (1, 4, 7, and 40 days old, respectively), fixed with an alcoholic solution of chloral hydrate, followed by hardening in 95 per cent alcohol with a few drops of ammonia.* Before impregnation the hearts were divided into blocks; after reduction of the silver the blocks were dehydrated, embedded in paraffin, and cut serially; the plane of sectioning varied according to the structure to be studied. The best views of the conductive system were obtained in frontal sections, 12 to 14μ thick. The material from the monkey consisted of the heart of a fully grown animal which was prepared in the same way except that a piece of the left ventricle was fixed with Bouin's fluid for routine staining.

The technique mentioned above does not impregnate all nerve fibers to the same degree. The axons of the sympathetic ganglion cells (sympathetic postganglionics) appear yellow to light orange, according to the length of impregnation; for this reason, namely, lack of contrast with the yellowish background of the preparation, they cannot be identified outside of the nerve bundles. All other nerve fibers, including the axons of the cells of the intrinsic cardiac ganglia (parasympathetic postganglionics), have greater affinity for the silver and

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*For further details of this technique see Nonidez.[2]

are stained dark brown to black.[2] The constancy of these differences, which have been verified experimentally for the sympathetic ganglia supplying the heart,[3] makes it possible to follow the distribution of the parasympathetic axons, an advantage not possessed by other silver impregnation methods. In the adult monkey the contrast between the weak argyrophilia of the sympathetic axons and the greater affinity for the silver of the other nerve fibers is even more marked than in the dog, and is also conspicuous in the peripheral nerves.* This shows that the differences noted above are neither restricted to the visceral nerves nor influenced by age.

Although the technique used is primarily for impregnation of nerve cells and fibers, it permits identification of other tissues without counterstaining. Striated muscle fibers are well stained, and the capillaries are more readily identified than in sections prepared with routine procedures. The connective tissue fibers are not ordinarily impregnated, but, when they are, they stain so diffusely that they cannot be mistaken for nerve fibers. In the particular case of the heart, the Purkinje fibers are well seen because of their very light impregnation, in contrast with the ordinary myocardial fibers which stain more deeply (Fig. 9).

II. OBSERVATIONS

As far as the inferior (or distal) parts of the system are concerned, my observations on the dog corroborate the classical ones of Tawara.[4] There is an atrioventricular node which is continued inferiorly into a main bundle (crus commune), and there are right and left bundle branches composed of Purkinje fibers. As will be shown presently, the node is richly supplied with nerve fibers, mostly axons of the ganglion cells of the subepicardial plexus, and this is in contrast with the inferior (distal) portion of the main bundle and right and left bundle branches and their ramifications, which are neither innervated directly by the vagus nor by the ganglion cells. Since the technique employed does not impregnate sufficiently the axons of the sympathetic ganglion cells, the problem of the sympathetic innervation of the conductive system is left unsolved. In addition to the atrioventricular node, there is a smaller sinoatrial node which is also supplied, although to a lesser extent, by parasympathetic nerve fibers.

The conductive system of the monkey follows the same plan as in the dog, but the main bundle and proximal portions of the right and left branches have numerous parasympathetic nerve endings. Typical Purkinje fibers are absent; instead there are fibers rich in sarcoplasm that resemble the transitional stages between the Purkinje elements and the ordinary myocardial fibers of the dog.

1. The Sinoatrial Node. a. Structure.—This node lies in the crista terminalis and consists of an elongated roundish mass (head) and a narrower portion (tail). It is best seen in very young puppies (Fig. 1, *A*). It has been described as a mass of irregularly anastomosed strands, separated by abundant connective tissue containing numerous

*The differential staining of the fibers in the peripheral nerves is very marked in preparations of the brachial plexus of an adult rhesus monkey.

capillaries.[5] My observations on serial sections of the hearts of very young puppies do not agree entirely with this description. Indeed, in very young hearts, the trabeculated portion is actually the area of transition between the ordinary myocardium and the node proper. The latter has a more compact appearance, and consists of frequently anastomosed fibers of myoblastic aspect, with few myofibrils; their nuclei vary somewhat in size and are so closely placed in some areas that they almost touch each other (Fig. 2). Between the fibers there are slender capillaries and connective tissue which presumably increases in amount with age.

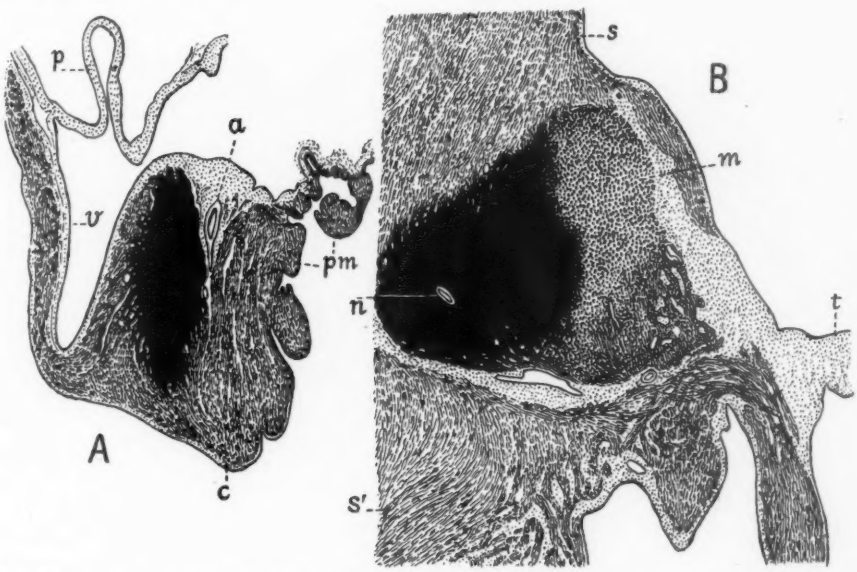

Fig. 1, *A* and *B*.—Camera lucida drawings showing the position of the sinoatrial and atrioventricular nodes, respectively, in a day-old puppy, drawn at the same magnification. Nodes, black. *a*, Artery supplying the crista terminalis, S-A node, and atrial wall; *c*, crista terminalis; *m*, main bundle (coarse stippling); *n*, nodal artery; *p*, pericardium; *pm*, pectinate muscles; *s*, *s'*, interatrial and interventricular septa, respectively; *t*, base of septal flap of the tricuspid valve; *v*, wall of the superior vena cava. Frontal series, posterior view of sections.

Irregular strands radiate from the node in every direction, but they are more numerous on its internal (mesial) aspect; many trabeculae invade the wall of the caval funnel, whereas others connect posteriorly with the muscular sheet that binds the atria together. As stated above, the strands or trabeculae represent the transition between the nodal tissue proper and the ordinary myocardium; accordingly, their fibers are richer in myofibrils and the nuclei are more scattered. Individual differences in the size and arrangement of the trabeculae may have led some authors to deny the existence of the node in adult hearts. Furthermore, the myoblastic fibers so clearly seen in the very young animal are capable of further differentiation with increasing age. On account of this, the S-A node of older puppies does not stand out as clearly as in the newborn, but careful study shows a lesser degree of

differentiation of its constituent fibers as compared with the ordinary myocardial elements. It is easy to understand, therefore, that to an observer who has not studied the heart of the newborn the differences noted may seem trivial.

The S-A node of the monkey occupies the same position as in the dog, but in the adult, at least, its fibers, although quite slender and wavy, contain more myofibrils, and their nuclei are somewhat more spaced. The trabeculated character of the node is more evident than in the puppy, and the spaces between the trabeculae contain larger amounts of connective tissue.

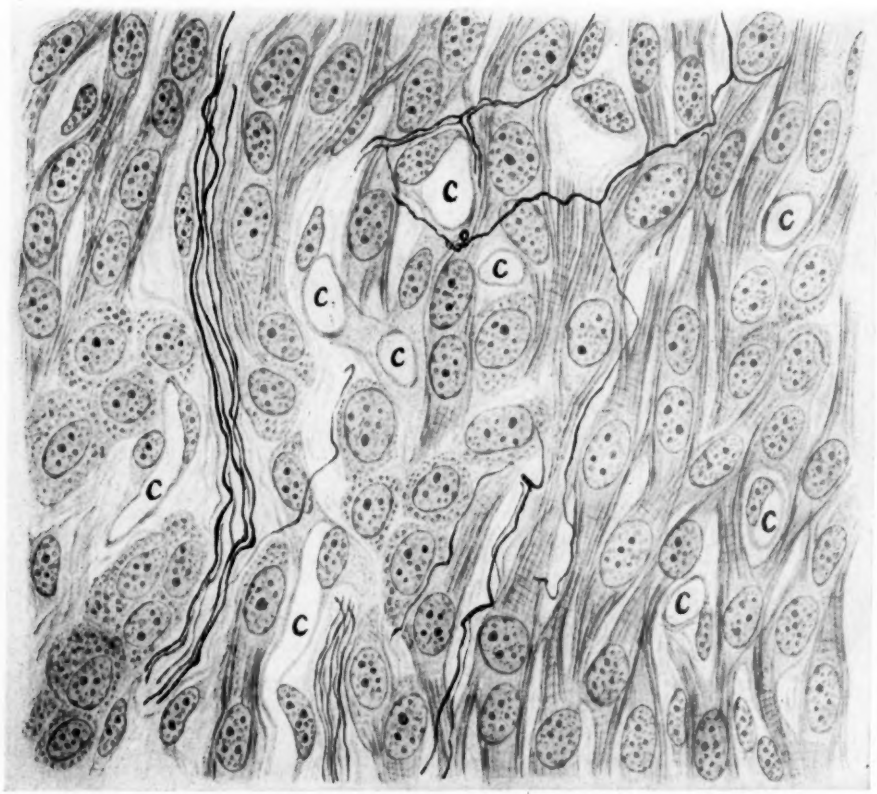

Fig. 2.—High-power drawing of a portion of the S-A node. Notice paucity and small diameter of the nerve fibers. The muscle fibers to the left of the figure approach the transitional stage, while those to the right are typical of the dense portion of the node. *c*, Capillaries.

b. Innervation.—The nerve supply to the S-A node is not as rich as might be expected, when one considers the wealth of nerve bundles in its vicinity. The bundles, as well as numerous ganglion cells, have been seen by several authors in diverse animals, mostly in routine slides; however, many of the nerve fibers in these bundles do not enter the node, but supply the ordinary myocardial fibers in the surrounding

region. The above statement refers only to the deeply impregnated parasympathetic postganglionics; the larger bundles also carry pale fibers (sympathetic postganglionics), but their final distribution could not be ascertained for reasons already mentioned.

With the technique used, the deeply stained nerve fibers to the node and juxta-nodal area can be traced to ganglia scattered in the extensive nerve plexus investing the caval funnel and extending under the epicardium of the intercaval space. Their distribution in the dog has been recorded by Bachmann,[6] Schurawlew,[7] and Nonidez.[8] Small cells predominate in the ganglia of the caval funnel.* The ganglion cells receive impulses through preganglionics coursing in the vagi. The existence of direct efferent vagal fibers is beyond experimental histologic demonstration because: (1) elimination of the axons of the ganglion cells would require destruction of all the ganglia in the vicinity of the node, and time should be allowed for degeneration of the axons (fourteen to twenty days); (2) even if the operation were successful, there would be left numbers of small afferent fibers which cannot be eliminated without section of the vagi, but this procedure would suppress at the same time the preganglionics and whatever direct efferent fibers may occur. Experimental evidence showing that the ganglion cells are the source of parasympathetic nerve fibers to the node is found in the work of Bachmann[6] and Heinbecker and Bishop,[9] and will be considered in the discussion.

The terminations of the parasympathetic postganglionics in the node do not differ from those previously described for the atrial musculature.[2] The finer branches end as minute single or double rings, "boutons," and small reticulated enlargements in contact with the surface of the muscle fibers. Swellings also occur along the twigs, and are probably as important for the discharge of stimuli as the terminal rings and enlargements. Nerve endings resembling the motor plates of skeletal muscle, as described by Blair and Davies,[10] do not occur in the S-A node of the dog and monkey.

Afferent nerve endings are present in close proximity to the S-A node. They resemble the neuromuscular organs (muscle spindles) of skeletal muscles. In the monkey (Fig. 3) they are more elaborate than in the cat and dog, in which they were first noticed.[8] These terminations are not numerous, and arise from thick myelinated fibers; their branches are wound around the muscle fibers of one or more bundles which run intramurally in the right atrium and are continuous with longitudinal muscle bundles in the wall of the superior vena cava. The finer branches of termination end as simple or double rings and lamellar enlargements of considerable size. Whether these perimuscular nerve endings belong to the conductive system is difficult to say. The constancy of their presence in the same position in the three species examined suggests that they function during some phase of

*Unpublished observations.

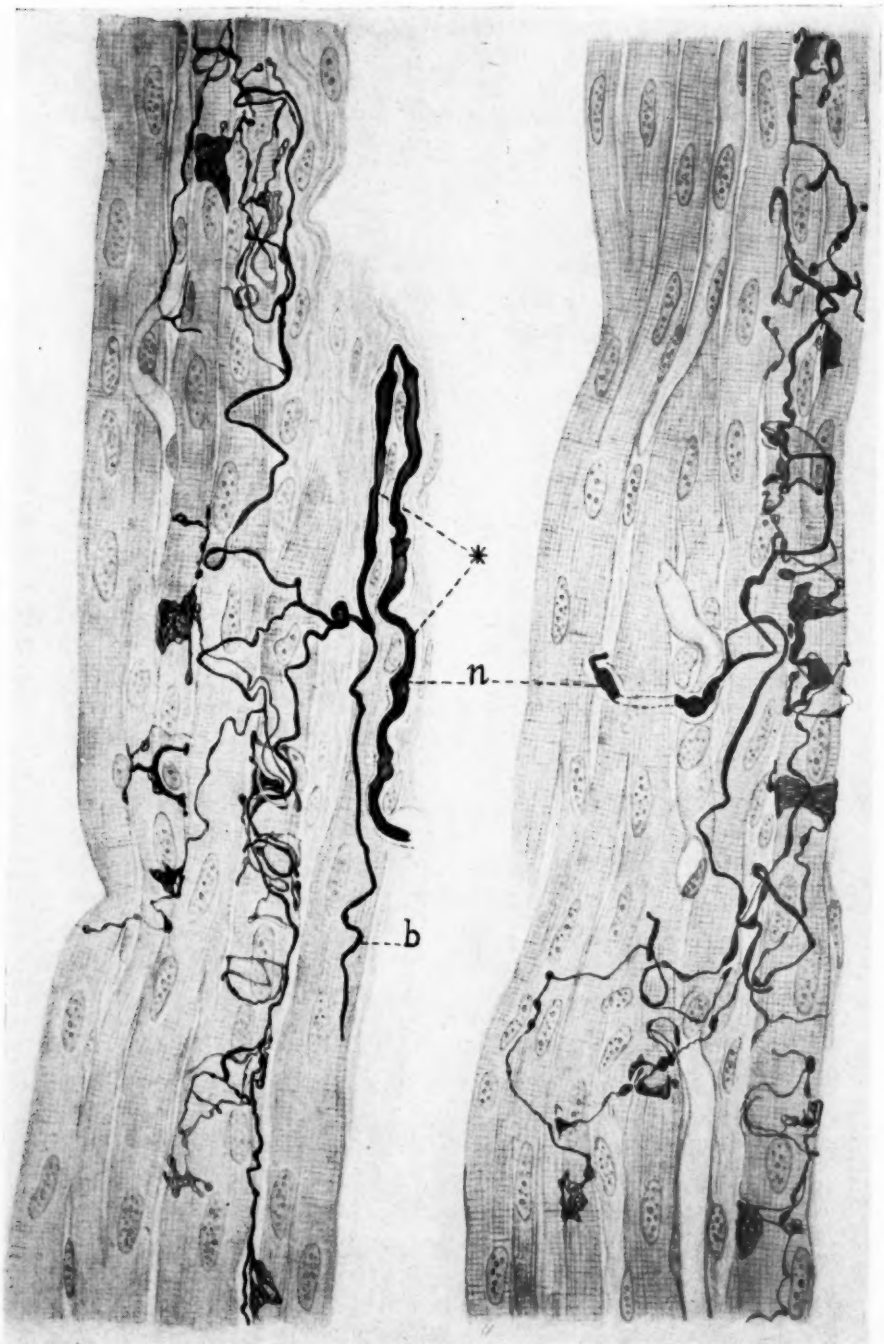

Fig. 3.—Perimuscular nerve endings, heart of adult rhesus monkey. *n*, Nerve fibers. The portion * and branch *b* in the drawing at the left were copied from the section following the one represented.

the cardiac cycle, and the view has been advanced that they are the nerve endings for the hypertensive reflex of De Waele and Van de Velde (Nonidez[11]). In the cat they persist after upper thoracic sympathectomy. In this animal, according to Pannier,[12] elaborate afferent nerve endings are also present in the nodal tissue, and similar terminations occur in the walls of the atria and auricles.

Meiklejohn[13] has described, in the monkey, Callithrix, complex nerve endings wound around muscle fibers. According to this author, "Some of the more complex endings surround a cluster of nuclei which appear to be muscle nuclei, but which are much more closely grouped than the nuclei of the surrounding muscle." "Very closely resembling some of the more complex endings described above, are the networks occurring in the course of some of the fibers. A small fiber sometimes breaks up in its course into a complex network, showing varicosities at the terminations and in the course of the fibrils. . . . Such a network appears to be a 'station' on the course of the fiber: the one shown at Fig. 13 could be traced through five sections 7μ thick" (p. 8). From this description (based apparently on transverse sections of the heart) it appears that the elaborate endings described by Meiklejohn were in all probability transverse sections of clusters of branches of the extensive terminations represented in Fig. 3 of this article; they are best seen in longitudinal sections of the heart, in which their true shape is displayed.

In concluding the description of the innervation of the S-A node, it must be stated that, in the older animals which were examined, nerve fibers around and within the node were still scarcer than in the very young animals. This is undoubtedly due to spacing of the nerve fibers as a consequence of the growth of the myocardium. Accordingly, in serial sections of the adult heart it is difficult to visualize the extent of the innervation and the distribution of the nerve endings. It is for this reason that the hearts of newborn or very young animals were used in the present study.

2. The Atrioventricular Node.—The A-V node is larger than the S-A node and has a richer parasympathetic innervation.

a. Structure.—In the newborn puppy, portions of the node proper and the main bundle appear side by side in frontal sections of the heart (Fig. 1, *B*). The largest portion of poorly differentiated nodal tissue occurs internal to the bundle (*m*), with which it is connected through gradual transitions. The node consists of (1) fibers with a myoblastic aspect, namely, short spindle or slightly branched anastomosed cells, with few myofibrils and oval or elliptical nuclei (Fig. 4), and (2) larger cells with round nuclei and clear cytoplasm, with variable numbers of faintly argyrophilic granules. The latter cells also occur in the bundle, in which they tend to form rows; they gradually change into the typical Purkinje fibers characteristic of the more anterior (distal) portions of the bundle and its branches, to be described presently.

The more superior regions of the bundle and node (i.e., those portions nearest the opening of the coronary sinus) are not clearly defined because they are continuous with bundles of ordinary myocardial fibers. Of special mention is a bundle which passes toward the right side along the posterior wall of the root of the aorta, because it may be an important path for impulses reaching the node and main bundle from the left atrium.

The delimitation of the A-V node is still more difficult in the rhesus monkey. The loosely reticulated portion, which, according to most descriptions, should be regarded as the node (Fig. 7, *n*) is actually the zone of transition between the atrial myocardium and the nodal tissue, and is less profusely innervated than the more compact portion which is continuous with the main bundle. The elongated nodal portion shows anastomosed fibers of variable diameter, some of which are rich in sarcoplasm; the cross striations of their myofibrils are more conspicuous than in the puppy (Fig. 8).

b. Innervation.—Contrary to reports by other authors,[10, 13] my observations on the A-V node clearly show that it has a richer innervation than the S-A node.* This discrepancy is probably due to the fact that the authors mentioned above used adult hearts, and also to the belief that the nerve bundles near the S-A node carry nerve fibers to this node, but in serial sections of the young heart it is evident that most nerve fibers in these bundles supply the atrial musculature, and that, as stated before, relatively few enter the S-A node proper. As to the use of adult hearts, it is to be remembered that the S-A node lies in the crista terminalis, where even in the adult it is easily accessible to the silver because of the thinness and relatively loose structure of the atrial wall, whereas the A-V node lies internally against the mass of dense connective tissue of the annuli fibrosi. Under such conditions the penetration of the silver in the region of the A-V nodes of adult hearts is more difficult than in the very young animal, in which the endocardium of the atrioventricular canal is much thinner than in the adult, and the connective tissue of the annuli less dense.

The parasympathetic nerve fibers ending in the node arise from ganglia located under the epicardium of the coronary sulcus and posterior atrial walls. Perinodal ganglia (present in the calf and sheep) are absent in the dog and monkey, but small groups of ganglion cells do occur within the interatrial septum in the vicinity of the node.

Fig. 4 gives an idea of the abundance of nerve branches and endings in the A-V node of the same (1-day-old) puppy from which Fig. 2 was taken. The nerve fibers and their branches form an elaborate plexus within the node. Reticulated swellings occur in the branches; in good

*Recent observations by E. W. Walls (Specialized Conducting Tissue in the Heart of the Golden Hamster [Cricetus Auratus], J. Anat. 76: 359, 1942) which appeared when the present article was ready for the press disclose a similar situation. According to this author, numerous nerve fibers could be traced into the substance of the A-V node; in contrast, the S-A node "has a poor nerve supply, no fibers or cells being demonstrable in the substance of the node."

impregnations the terminal rings and minute club-shaped terminal enlargements of the finer branches of the arborizations are clearly seen. In many instances the terminal rings and enlargements occur in contact with the myoblastic elements of the node.

The nerve fibers which branch within the node vary in diameter. When their relative thickness is taken into account, one is tempted to believe that the thicker fibers are afferent, but the type of their terminal arborization is not characteristic enough to permit a positive statement. Perimuscular endings of the type found in the vicinity of the S-A node (Fig. 3) do not occur in the region of the A-V node.

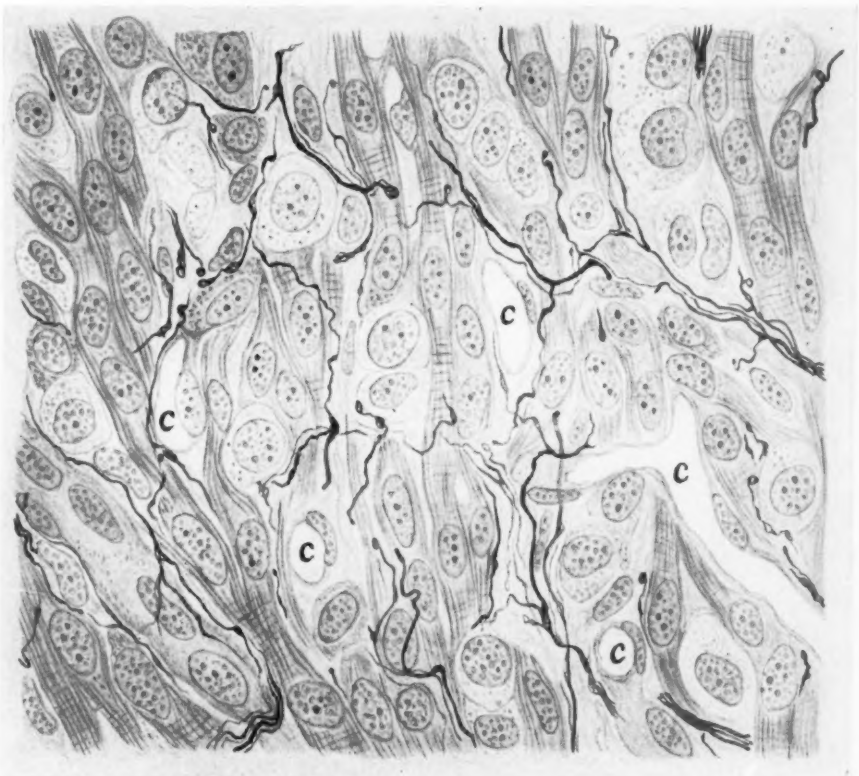

Fig. 4.—High-power drawing of a portion of the A-V node, showing nerve terminations. Same puppy as in Fig. 2, but slightly less magnified.

In the monkey the nerve fibers branch not only within the A-V node, but also in the main bundle and proximal portions of its two branches. The fibers divide repeatedly and end as in the dog. The trabeculated or intermediary portion has fewer nerve fibers and endings.

3. The Main Bundle (Crus Commune). a. Structure.—As already stated, the A-V node of the dog is continuous with a bundle composed of fibers identical with those described for the node, and, in addition, Purkinje fibers; the latter predominate in the inferior (or distal) half

of the bundle. In serial sections this bundle is seen to divide into right and left branches. As shown by Tawara, the main bundle runs in the midst of the narrow membranous portion of the septum. This is clearly seen in frontal sections of the heart. Fig. 5 is a camera lucida sketch of a section of the heart of a 40-day-old puppy, and shows the origin of the left bundle branch (*b'*). Since the series in this case begins posteriorly, the branch under consideration, running subendocardially on the left surface of the interventricular septum, appears

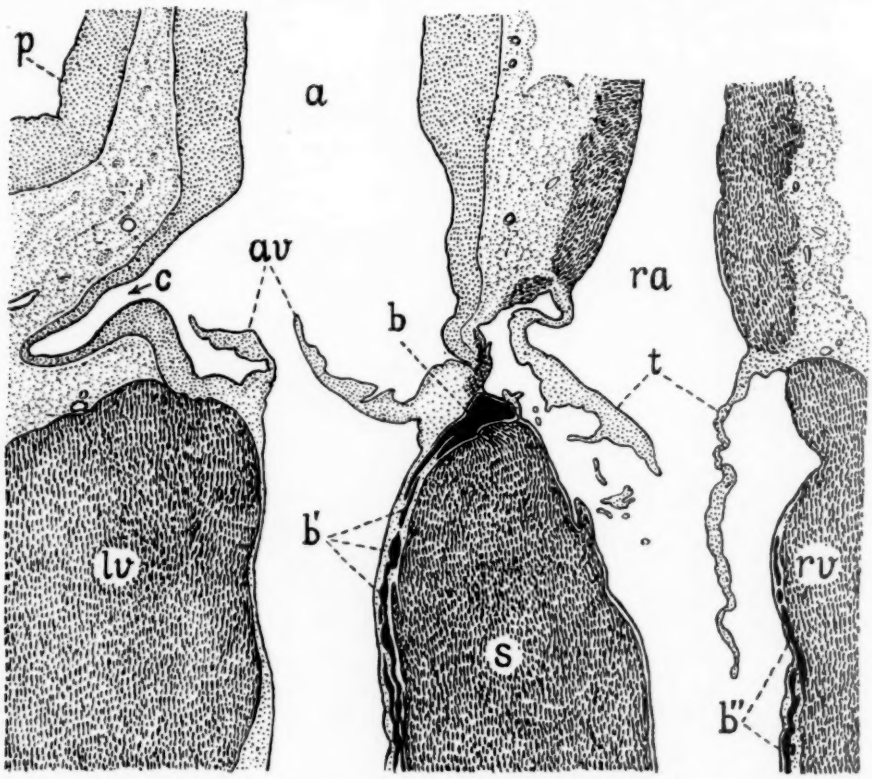

Fig. 5.—Camera lucida drawing showing the main bundle (*b*) in the membranous portion of the interventricular septum (*s*), the left bundle branch (*b'*), and the distal portion of the right bundle branch (*b''*) in the wall of the right ventricle (*rv*). *a*, Aorta; *av*, aortic valves; *c*, left coronary artery; *lv*, wall of left ventricle; *p*, wall of pulmonary artery; *ra*, right atrium; *t*, tricuspid valve. Posterior view of a frontal section of the heart, 40-day-old puppy.

toward the left of the figure. The right branch is not seen at this level because it is actually the continuation of the main bundle beyond the point of origin of the left branch; it divides into branches which continue distally within the septum and finally reach the surface of the right ventricle (*rv*), ascending subendocardially toward the atrioventricular orifice, in the vicinity of which they can still be detected (*b''*). The drawing is practically identical with Tawara's Fig. 7, Tafel I; the only difference is that the figure by this author was copied from a

series beginning anteriorly, i.e., the left branch appears toward the right of the observer.

Fig. 6 is a photomicrograph of the main bundle (*b*) in the same section from which the preceding figure was made. Even though it lacks detail, the contrast between the bundle (composed of Purkinje fibers) and the ordinary myocardial fibers of the interventricular septum (*s*) is quite marked. The presence of a space between the periphery of the bundle and the surrounding tissue is also evident.

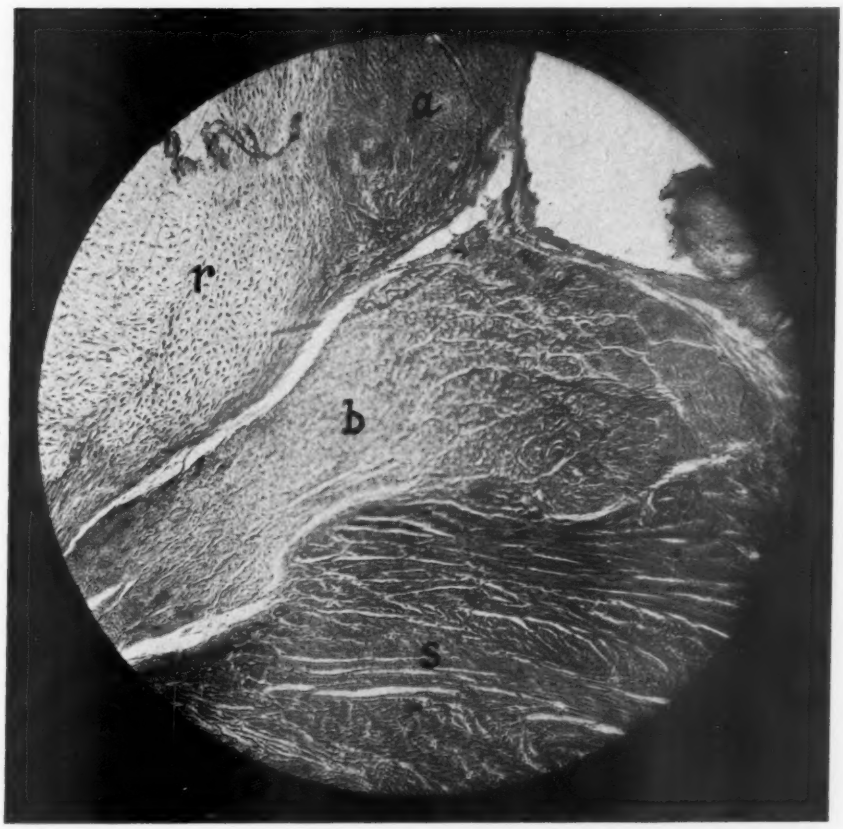

Fig. 6.—Photomicrograph of the main bundle (*b*) from section in the preceding figure. *a*, Atrial musculature; *r*, fibrous ring; *s*, musculature of the interventricular septum. Notice definite space between the bundle and the surrounding tissues.

Study of serial sections shows that, in this puppy, at least, the only connection between the atrial and the ventricular musculature is the main bundle. The existence of secondary connections in other puppies is within the bounds of possibility; if, as claimed by most investigators, the conductive system differs functionally from the ordinary cardiac musculature, it is questionable whether these connections would influence the physiologic properties of its tissue, but they may attenuate or even suppress the symptoms expected after block of the main bundle.

The above statements apply also to the monkey. Fig. 7 shows the A-V node and bundle (solid black) in the membranous portion of the septum (stippled). *A* shows the point of origin of the left branch (*b″*), while *B* shows also the right branch (*b′*). In contrast with the main bundle of the puppy, the corresponding structure of the monkey is more differentiated in the sense that the muscle fibers have more myofibrils and a correspondingly smaller amount of sarcoplasm; however, fibers with fewer myofibrils, a greater amount of sarcoplasm, and larger nuclei also occur in the bundle (Fig. 8).

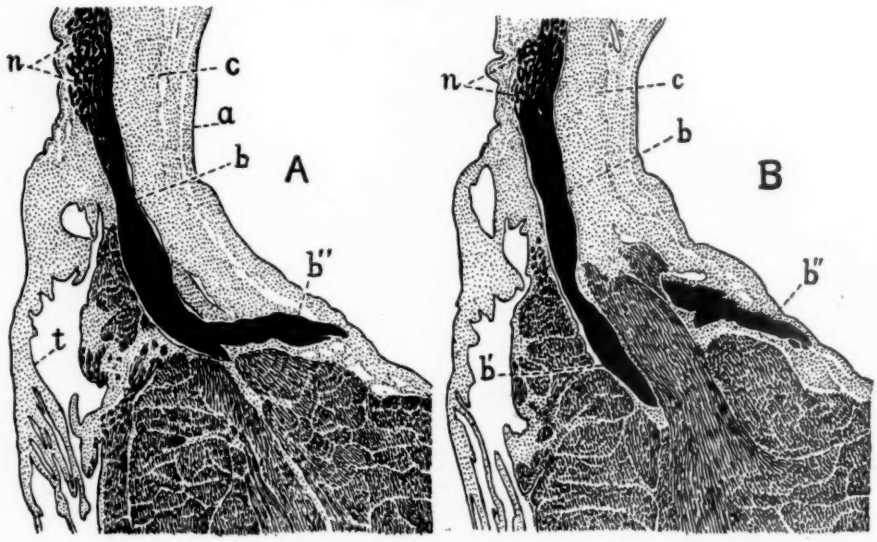

Fig. 7, *A* and *B*.—Camera lucida drawings of the A-V node, main bundle (*b*), and right (*b′*) and left (*b″*) bundle branches of an adult rhesus monkey. The space between the bundle and the surrounding tissues has been indicated. *a*, Wall of the root of the aorta; *c*, connective tissue of the pars membranacea of the interventricular septum; *n*, trabeculated portion of the A-V node; *t*, septal flap of the tricuspid valve. From a transverse series of the heart.

b. Innervation.—The extent of the parasympathetic innervation of the main bundle is different in the two animals studied. In the dog the nerve fibers are restricted to the superior part of the bundle (i.e., the portion next to the node) whereas in the monkey, as noted by Meiklejohn,[13] nerve fibers and their arborizations occur throughout the bundle (Fig. 8) and course for some distance within the right and left branches, which they may reach through devious paths. It would seem, then, that crushing the A-V node and bundle in the monkey may not completely abolish the chronotropic effect of the vagus on the ventricular musculature, for numbers of nerve fibers from ganglia in the coronary sulcus may escape injury, whereas, in the dog, the operation suppresses vagal influence to the extent that in about 50 per cent of the cases it can be demonstrated only after eserine.[14] The type of nerve endings that were found in the main bundle of the monkey is essentially the same as in the other portions of the conductive system.

4. The Right and Left Bundle Branches and Their Ramifications.—The structure of these branches differs in the two species studied. In the dog their component fibers resemble closely the Purkinje strands of the calf, sheep, etc., whereas, in the monkey, the differences between the Purkinje elements and the ordinary myocardial fibers are less marked.

Fig. 8.—Nerve branches and terminals in the A-V bundle near the node, under high magnification. Same as in preceding figure.

a. Structure.—In the dog the branches divide repeatedly until an elaborate system of subendocardial strands is formed. The most typical Purkinje fibers occur immediately beneath the endocardium (Fig. 9, left). They have swollen portions which are separated from each other by constrictions. The swollen portions usually contain two nuclei which may be closely placed or separated; the nuclei often have a crescentic shape and may appear crenated. Distinct perinuclear spaces are seen in most segments. Each of the latter is crossed by myofibrils, gathered into definite bundles or running more or less independently.

The myofibrils of the different segments are continuous; as they pass through the constricted portion they show deeply stained granular enlargements, well illustrated by Tawara. Indeed, the Purkinje fibers in my preparations agree in every detail with those represented by this author in his Figs. 2, 3, and 5, Tafel V, taken from serial sections of the heart of a 3-day-old puppy. They also correspond to the elements labeled as Purkinje fibers in the photomicrographs published by Abramson and Margolin.[15]

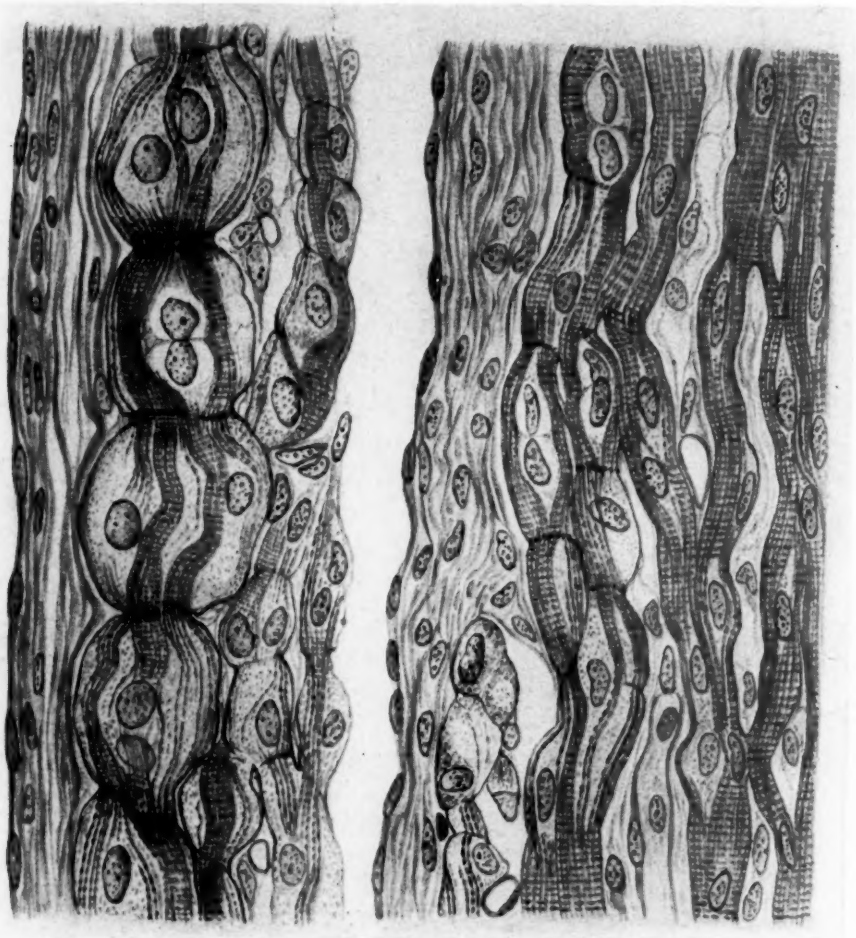

Fig. 9.—(Left) Subendocardial Purkinje fibers and (right) their transition into ordinary myocardial fibers. Notice absence of nerve fibers. Same puppy as in Figs. 5 and 6.

Immediately beneath the large Purkinje fibers there are strands composed of smaller segments containing one or two nuclei and fewer myofibrils (Fig. 9, left). These thinner fibers gradually connect with the ordinary cardiac fibers, either subendocardially or in the deeper

portions of the ventricular wall. The connection between the two types is better seen in the drawing at the right of the figure. Some of the slender segments have two closely placed nuclei of more or less crescentic shape, enclosed within a perinuclear space; the myofibrils seem more numerous and have thickenings as they pass from segment to segment of the fibers. These thickenings are not present in the ordinary cardiac fibers; the intercalated discs of the latter do not show in silver impregnations.

In the dog, at least, there can be little doubt that, although the Purkinje strands run predominantly parallel with the inner ventricular surface, they eventually connect with the myocardium. The term "embryonic," applied by Todd[16] to the fibers rich in sarcoplasm and poor in myofibrils, is unfortunate because the muscle fibers of the atria and ventricles do not go through a stage corresponding structurally to the Purkinje fibers of postnatal life. Indeed, the formation of the Purkinje elements in the embryo is a process of gradual differentiation which is continued to some extent in early postnatal life.* In newborn and very young puppies the Purkinje fibers are less distinct and thinner than in the older puppies.

The monkey lacks the typical Purkinje elements that are seen in the puppy, but the ramifications of the right and left bundle branches consist of fascicles which differ from the ordinary myocardial fibers. The Purkinje strands in this animal are composed of fibers of irregular size, embedded in connective tissue. Most fibers have a large amount of sarcoplasm which contains numerous spherical, closely placed, transparent granules appearing as rings in optical section; these granules do not occur in such an abundance in the ordinary cardiac muscle fibers. The nuclei of the Purkinje elements are often quite irregular in shape, and may have a crenated aspect due to pressure of the sarcoplasmic granules against the nuclear membrane. In the larger fibers the myofibrils occur in small bundles or run independently from each other in the abundant sarcoplasm, but in most cases they occupy the periphery of the fiber. These structural details, plainly visible in silver preparations, are still better seen in sections stained with the Masson trichromic technique (Fig. 10).

b. Innervation.—As is the case with the superior part of the main bundle, the right and left bundle branches of the dog are not supplied by parasympathetic nerve fibers. That absence of the latter is not the result of faulty impregnation is shown by the fact that the parasympathetic plexus in small arterial branches which occur here and there in the vicinity of the Purkinje strands is well impregnated. The occurrence of sympathetic innervation cannot be either denied or affirmed with the technique used, but the paucity of pale fibers in the

*This opinion is based on study of the hearts of calf embryos in the splendid embryologic collection of the Department of Zoölogy of Cornell University. The author is indebted to Dr. B. F. Kingsbury and Dr. H. B. Adelmann for courtesies extended to him during his visit to their laboratory.

vicinity of the branches indicates that the participation of the sympathetic in the innervation of the Purkinje strands must be limited.

As already stated, in the monkey, parasympathetic fibers extend into the proximal (or initial) portions of the bundle branches. The fibers course in nerve bundles which become progressively smaller and finally disappear. The more distal portions of the conductive system in the ventricles lack a parasympathetic nerve supply.

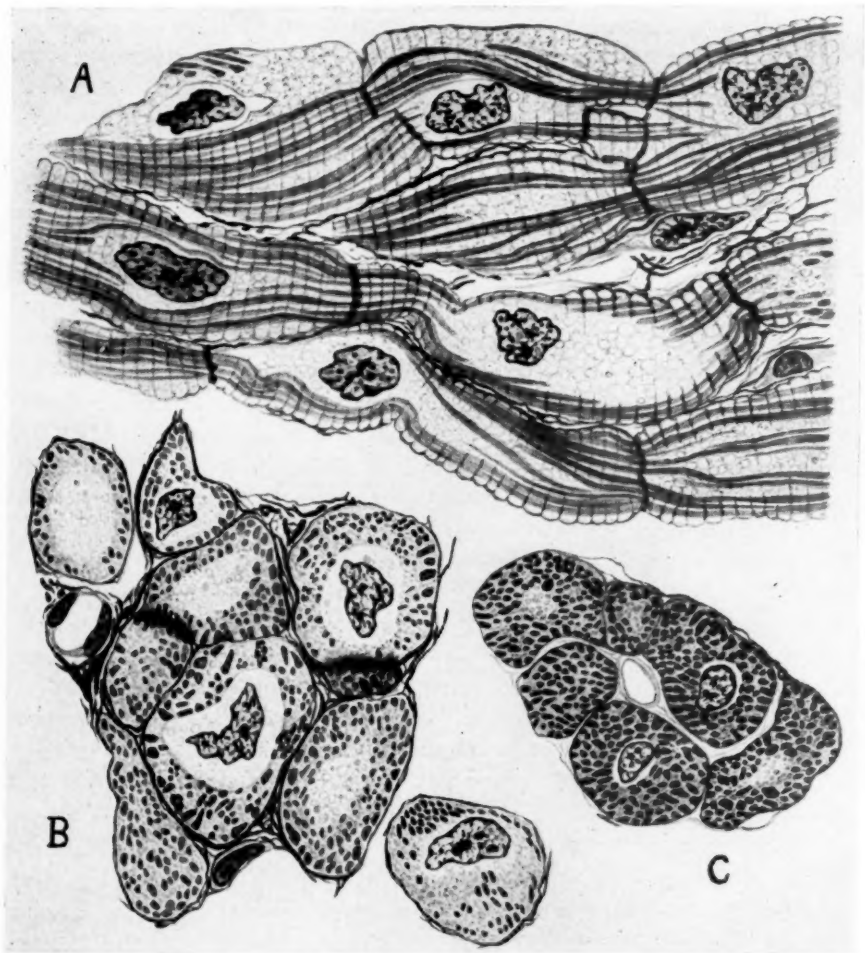

Fig. 10.—Rhesus monkey. *A* and *B*, Purkinje fibers of the left bundle branch in longitudinal and transverse section, respectively; *C* transverse section of ordinary myocardial fibers. Bouin's fluid; Masson trichromic technique.

Nerve terminations among the Purkinje fibers have been described in the calf and sheep by all authors who have studied the innervation of the heart in these animals. According to Vitali,[17] the nerve fibers are very numerous, and, through multiple branchings, they give rise to a complex plexus enveloping the Purkinje strands; he regards these

fibers as afferent. A study of the figures by this author leads me to believe that the fibers described by him are not nervous, but that they belong to the argyrophil reticulum which is present everywhere in the heart.

5. The Parasympathetic Innervation of the Atrial Myocardium.—An interesting feature of the nerve supply to the heart is the participation of the parasympathetic nerve fibers (axons of the neurons of the intrinsic ganglia) in the innervation of the atrial and auricular myocardium. This is in contrast with the nerve supply to the myocardium of the ventricles, which is by means of sympathetic postganglionics from the middle cervical, stellate, and upper thoracic ganglia. Fibers arising from these ganglia also reach the atria, but, with the technique used, it is impossible to learn their ultimate destination.

The existence of ganglion cells to supply the cardiac muscle fibers is known through the researches of Dogiel,[18] Woollard,[19] Lawrentjew,[20] and Nonidez.[2] Woollard expressed the view that the greater part of the parasympathetic nerve fibers supply the supraventricular portions of the heart. This has been confirmed with the chloral hydrate-silver technique because of the strong affinity of the axons of the ganglion cells for the silver. In the monkey, in which the initial (proximal) portions of the right and left bundle branches are supplied by parasympathetic postganglionics, the contrast between these portions and the ventricular myocardium is quite marked. I have been able to follow the right bundle branch in serial sections of the interventricular septum, and, although deeply stained nerve fibers are seen ending within the branch, in no case have I seen terminations in the surrounding myocardial fibers.

The mode of termination of the parasympathetic nerve fibers on the atrial myocardium is similar to that described for the nodes; contact with the muscle fibers is effected by means of terminal and subterminal rings, minute club-shaped dilatations, and reticulated swellings (Nonidez,[2] Figs. 8 to 12). The terminations of the sympathetic postganglionics in the ventricles (as seen with other impregnation techniques) are very similar to those of the parasympathetic fibers.

The branches of the parasympathetic postganglionics ending on the atrial myocardium do not seem as numerous in the adult as in the hearts of very young animals. Whether branching of the nerve fibers increases in complexity after birth is difficult to say, but my impression is that a good deal of spacing takes place.

III. DISCUSSION

These observations on the structure and distribution of the conductive system are in substantial agreement with views currently held. Indeed, in young hearts it is possible to follow the distribution of the conductive system better than in the adult because serial sections can be obtained without an undue amount of labor, and the distances in-

volved are shorter. The same can be said of the hearts of small animals. In impregnations of frozen sections of the entire heart of the rat with the Bielschowsky-Gros technique, Lawrentjew and Gurwitsch-Lasowskaja[21] found that the A-V node and main bundle take the silver more rapidly than the surrounding structures, and thus can be readily detected under low magnifications.

Although there are reports on the innervation of the conductive system,[10, 13, 17, 19, 21] the techniques used by these authors did not permit differentiation of the parasympathetic from the sympathetic innervation. With the procedure employed by the present writer it is possible to identify and, in favorable cases, trace the parasympathetic postganglionics to their terminations. As already stated, some of these fibers (axons of the neurons of the intrinsic cardiac ganglia) end in the nodes and atrial myocardium, whereas others course with the branches of the coronary arteries in the ventricles, as well as in the atria. At present it is impossible to say whether there are direct efferent vagus fibers, for reasons already stated. The physiologic evidence, however, shows that destruction or paralysis of the ganglia of the S-A junction of the dog leads to a loss of chronotropic influence.[6] Similarly, in the cat, nicotine injection not only prevents the chronotropic effect, but it also suppresses the inotropic.[9]

The relatively small numbers of myofibrils, greater abundance of sarcoplasm, and presence of glycogen in the Purkinje fibers have been regarded as important structural factors in the rate of their conduction and refractory period. In other parts of the system, specially in the nodes, the fibers are finer and their glycogen content smaller; indeed, the finest fibers and lowest glycogen content are said to occur in the A-V node, and this has been invoked to explain the slower conduction through this structure.[22] However, recent observations by Goss[23] on rat embryos show that the pause between the atrium and ventricle already occurs in the early heart before differentiation of the conductive tissue has taken place, and that it approximates the adult value. In the light of these observations, it seems probable that the role of the rich parasympathetic innervation of the A-V node is a subsidiary one, i.e., it increases the A-V interval upon vagal stimulation. Since the nerve terminals are more numerous than in the S-A node, the greater influence of the vagus on the A-V node[24] and the production of block upon electrical excitation of this nerve can be accounted for. Similarly, we would find an explanation of the A-V block induced by digitalis in cases of auricular fibrillation, and of the effect of morphine in producing a similar effect through central excitation of the vagus.[25] The injection of pitressin or neosynephrin frequently interferes with conduction; the reflex slowing occurs via either vagus, but only the nerve on the left side exerts sufficient effect on A-V conduction to produce block,[26] a result which is in accord with

the histologic observations, for most of the nerve supply to the A-V node and bundle is from ganglia receiving preganglionics from the left vagus. Of further interest is the coincidence of the area of richest innervation of the A-V node of the dog with the "susceptible region" of Lewis, White, and Meakins.[27]

Another interesting feature is the absence of parasympathetic innervation of the lower (or distal) portions of the conductive system, which are lodged within the septum and ventricular walls. In the dog this is also true of the main bundle and the bundle branches, whereas, in the monkey, the proximal part of the latter contain nerve endings. It has been claimed that, after destruction of the canine A-V node and bundle, the vagus still exerts an influence on the idioventricular rhythm. However, Jourdan and Froment,[14] who have reported this effect, admit that in about 50 per cent of the dogs the influence was so weak that it could be detected only after the injection of eserine. They accordingly suggest that vagus impulses reach the ventricles through devious paths. That the vagus normally exerts little or no action on the ventricles is now generally accepted. Furthermore, the experiments of Wiggers,[28] carried out in the course of many years, show that vagal excitation fails to abolish ventricular fibrillation produced in various ways.

As noted before, the axons of the neurons of the intrinsic cardiac ganglia (parasympathetic postganglionics) are widely distributed throughout the heart, but the only muscular structures supplied by them are to be found in the supraventricular regions. In addition to the postganglionics ending in the conductive system, there are fibers which establish contact with the ordinary myocardial fibers of the atria and auricles (appendages). The separate chronotropic and inotropic effects which follow excitation of the vagus thus rest on an anatomic basis. Heinbecker and Bishop[9] have shown that, during recovery from nicotine poisoning, stimulation of the vagus of the cat causes a slowing of the heart before the inotropic susceptibility has been recovered. This they have interpreted as indicating that there are nerve fibers which cause the chronotropic depression, whereas others produce the inotropic effect only. In either case, transmission of the nervous impulse is through ganglion cells.

The parasympathetic innervation of the S-A and A-V nodes, respectively, accounts for the marked influence of the vagi on conduction. Whether there is sympathetic innervation of the nodes could not be ascertained with the technique used in these studies. The same can be said in regard to the possible occurrence of sympathetic terminations in the atrial myocardium; should they be present, then the atrial muscle fibers would have a double innervation, as opposed to those of the myocardium of the ventricles, which are supplied solely by the sympathetic. The existence of a parasympathetic innervation of the supra-

ventricular myocardium may be related in some way to the absence of specialized muscle fibers connecting the nodes.

SUMMARY

1. A study of the impulse conducting system in the hearts of puppies and one rhesus monkey, prepared with the chloral hydrate formula of the Cajal silver nitrate technique, has confirmed the observations of previous investigators. In addition to the S-A and A-V nodes (Fig. 1), there is a distinct main bundle (Figs. 5, 6, and 7) which divides into right and left bundle branches. The latter and their ramifications are composed of swollen fibers, with small numbers of myofibrils, abundant sarcoplasm, and irregular nuclei. These fibers connect at various levels with the musculature of the ventricles (Fig. 9, right); in the puppy they resemble closely the typical Purkinje fibers of the calf, sheep, etc. (Fig. 9, left), whereas, in the monkey, they are less differentiated but nevertheless quite conspicuous (Fig. 10, *A* and *B*).

2. The S-A and A-V nodes, respectively, are supplied by axons of neurons of the intrinsic cardiac ganglia (parasympathetic postganglionics), but the nerve terminals are much more numerous in the A-V node (cf. Fig. 2 with Fig. 4). Whether there is a sympathetic nerve supply to the nodes could not be ascertained because the technique used does not impregnate sufficiently the sympathetic postganglionics.

3. The main bundle and bundle branches of the dog lack parasympathetic nerve endings. In the monkey these nerve terminals occur not only in the main bundle (Fig. 8), but also in the proximal portions of the right and left bundle branches. Parasympathetic nerve endings are absent in the ramifications of the bundle branches in the two species.

4. The rich parasympathetic nerve supply to the A-V node, as compared with the innervation of the S-A node, may account for such phenomena as the production of A-V block through electrical stimulation of the vagus, the similar effect produced by morphine, by digitalis in cases of auricular fibrillation, etc., and, in general, the greater influence of vagal stimulation on the A-V node.

5. The existence of a parasympathetic innervation of the ventricles, suggested by the effect of excitation of the vagus after the A-V bundle has been crushed, is questioned. The variable effects on the idioventricular rhythm reported by Jourdan and Froment cannot be explained on an anatomic basis.

6. The anatomic basis for the inotropic effect of the vagus is indicated by the existence of parasympathetic nerve endings in the atrial and auricular musculatures.

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CAPILLARY STUDIES IN MIGRAINE; EFFECT OF ERGOTAMINE TARTRATE AND WATER DIURESIS

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INTEREST in the phenomena underlying attacks of migraine has led to attempts to explain the mechanism involved. Graham and Wolff[1] were able to show that dilatation and increased amplitude of pulsation of the branches of the external carotid artery occurred during the attack, and, because reduction of the pulsation relieved headache, concluded that this fact was important to the mechanism of production of an attack. Kennedy[2] and others believe that local edema in the brain substance might be the cause of the attack. These two concepts are, a priori, not contradictory, in that, with increased pulsation, arteriolar dilatation may be inferred, and, under these circumstances, fluid might more readily pass through the walls of capillaries. Since exchange of fluid substances between the blood and the tissues occurs chiefly through the endothelial wall of the capillaries,[3-5] it was believed that study of capillary behavior in migraine might be fruitful.

The capillaries of the surface of the skin, as viewed by direct microscopy in man, vary in different areas. Morphologically, two main types are recognized. Over most of the surface of the body, the peripheral vessels are arranged in a network (rete mirabile).[6, 7] The second type forms a so-called terminal circulation, the vessels of which are referred to as "end capillaries." In such regions as the base of the cuticle of the fingers and toes, the skin over the tibia,[8] and the gingival papilla[9] there is a fairly regular and horizontal arrangement of the loops. This permits observation of the blood flow through portions of the capillary which may be distinguished as an arterial limb, a venous limb, and an intermediate part connecting the two, often referred to as the transitional limb.

In order to describe as objectively as possible the appearance of surface capillaries, the following observations have in each instance been commented upon:

1. Form of the individual capillary loops and arrangement in the field.
2. Diameters of the arterial, venous, and transitional limbs.
3. Occurrence of the blood flow and, when present, its speed and regularity.

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4. Visibility of the vessels in the deeper layers of the arterial and venous limbs and the subpapillary plexus.

5. Distinctness of the capillary outline.

Although most of these characteristics have been referred to extensively in the literature, variation in the distinctness has generally been regarded as caused by the specific nature or character of the skin, or to technique, when indirect illumination was used. Deutsch[10] has, however, very recently reported a direct relationship between decreased visibility and increased permeability of the capillaries.

METHOD

The first report of direct observation of the capillaries of the human skin was published by Lombard,[11] in 1912. Cedar oil was placed on the surface of the skin at the base of the cuticle to obtain a homogenous refracting medium, a cover glass was placed upon the oil, and the field was illuminated from the side. The basic principles of this method have been used up to the present time, and have been modified only in that the use of the cover glass has been dispensed with, the illumination improved, and special microscopes devised.

Certain limitations exist in using microscopic examination of capillaries as a guide to the nature of vascular responses: (1) It is subjective. This defect can be remedied to a certain extent by employing a camera, either still or moving, but, even here, interpretation is difficult. This is true especially with regard to distinctness of outline because of the possibility of shift in position during the taking of a picture. (2) It takes account of so few of the many capillaries involved in a vascular pattern. (3) It can be employed only on or very near the surface (skin or mucous membranes). For our purpose it was found advantageous to employ the base of the cuticle for studies of the skin, and the inner surface of the lower lip for studies of the mucous membranes. These sites were chosen because the regions are readily accessible to the objective lens of the microscope, the arterial and venous limbs of the capillaries can be observed over a greater distance, and because they are "end capillaries."

The source of light was either an automatically adjustable, air-cooled electric light, equipped with heat absorbing glass filters, or a carbon arc lamp and a water-cooling cell filled with 1 per cent nickel chloride solution. For the study of mucous membranes the "Ultrapak" device was most serviceable. Observations were made with magnifications of 60 or 70 diameters. For direct photography of the field, a beam splitting mechanism was used.

The data in this report were obtained from the examination of 118 patients (of whom 108 were photographed) in the Migraine Clinics at Bellevue Hospital and New York University College of Medicine.

OBSERVATIONS

Preliminary observations on patients during migraine attacks indicated the occurrence of a regular tendency to indistinctness or "blurring" of the capillary outline; this was less marked during the interval between attacks. Particular attention was thenceforth given to the observation of this phenomenon; since the conditions of observation

were relatively constant, it seemed likely that changes in distinctness might indicate a change in physiologic state. Indistinctness of the capillary outline was also observed in women during menstruation, and occasionally in other persons.

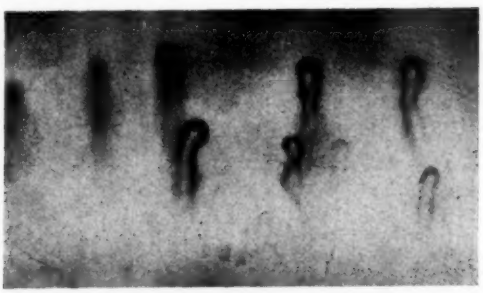

Fig. 1*A*.—"Normal" capillary loops photographed in the skin at the base of the cuticle of a healthy young adult male. Note that the hairpinlike forms have arterial limbs narrower than the transition and venous limbs. There are a few slight convolutions and single crossings.

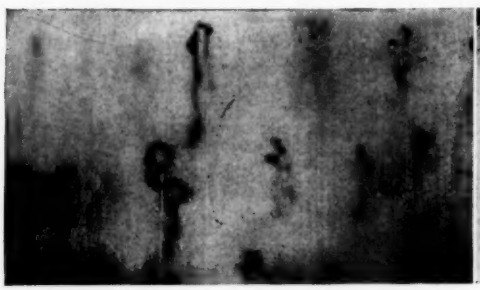

Fig. 1*B*.

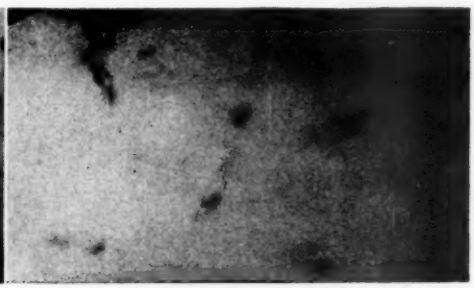

Fig. 1*C*.

Fig. 1*B*.—Capillary loops in the skin at the base of the cuticle of a 42-year-old female migraine patient, who also showed marked clinical signs of an endocrine disturbance (i.e., obesity, hirsutism, oligomenorrhea). Note that the capillaries show many of the changes specified as modifying the basic characteristics of the loop. Compare with Fig. 1*C*.

Fig. 1*C*.—Capillaries photographed in the interproximal papilla of the gingiva adjacent to the oral mucosa, of the same patient as shown in Fig. 1*B*. Note the presence of very similar changes.

Of the total of 118 migraine patients who were studied, repeated observations, on which this report is based, were made on 98. We observed differences in the form of the capillaries of these patients which may be appreciated best by comparison with the hairpinlike form of normal end capillaries (Fig. 1*A*). The appearance of the loop differed from the normal in its basic characteristics (Fig. 1*B*) in 88, or roughly 90 per cent, of the patients. These differences consisted of an increase in tortuosity of the limbs of the capillary loop, increase in the number of crossings, and the occurrence of knobbings in the different limbs. Variations in diameter of the different limbs, of long or short duration, occurred in 78, or about 80 per cent, of the patients. Differences in appearance and variations in width were found to be present simultaneously in 63, or about 65 per cent, of the patients. Similar deviations from the normal were found in the capil-

laries of the mucous membranes of the inner surface of the lower lip in 22 cases (Fig. 1*C*).

The blurring was found to be present during migraine attacks and absent or diminished during the headache-free interval in over three-fourths of the cases. The state of visibility varied even during the period of a single observation. The distinctness of the capillary was influenced by intravenous injection of ergotamine tartrate during an attack, the pattern of which is described later in this paper. Simultaneous observations were made on the capillaries of the skin at the base of the cuticle and on the mucous membranes of the mouth, and showed parallel changes. In any one observation, the mechanical setup remained unaltered throughout, and comparisons were made with the sharpest focus obtainable in the given field.

EFFECT OF EGROTAMINE TARTRATE UPON THE SURFACE CAPILLARIES IN MIGRAINE ATTACKS

Numerous observations[12-16] tend to show that ergotamine tartrate is effective in terminating the migraine attack. According to Lennox and Leonhardt,[17] the beneficial effect is due, at least in part, to an increase in arterial tone, arterial pressure, and rate of blood flow, together with a decrease in blood volume. Graham and Wolff[1] consider migraine to be directly related to the amplitude of pulsation of branches of the external carotid arteries, and relief from the attack by ergotamine was correlated with constriction of these arteries and reduction in amplitude of their pulsation.

METHOD

The peripheral capillary effect of an intravenous injection of 0.25 and 0.5 mg. of ergotamine tartrate* during the migraine attack was watched under the microscope, and photographs were made in twenty-three instances in sixteen patients. During the period of observation the patient was in the recumbent position, with the hand extended at approximately the heart level.

OBSERVATIONS

Characteristic capillary changes were observed to follow injection of the drug in a specific sequence.

Two to five minutes after the injection, the original "blurring" tended toward alternation between clearing and indistinctness. During this interval pronounced variations in diameter also took place. The indistinctness tended to increase with nausea. Eight to fifteen minutes after the injection, the capillaries appeared much clearer and narrower, and subjective relief was simultaneously experienced by the patient. Subsequently, the distinctness of the capillary outline again varied markedly. Thirty to forty-five minutes after the injection, the loops again became blurred.

*The ergotamine tartrate was "Gynergen" (Sandoz).

It has been indicated in the previous section that the capillaries of the skin at the base of the cuticle and on the inner surface of the lower lip behaved similarly as to changes in form and degree of visibility. Simultaneous observations and photographs in these sites made in two instances after ergotamine tartrate injections during migraine attacks (Figs. 2*A*, *B*, *C*, *D*) showed that the onset, duration, and sequence of the modifications, as noted above, coincided throughout in the two regions.

Fig. 2*A*.

Fig. 2*B*.

Fig. 2*A*.—Capillary loops in the skin at the base of the cuticle of an adult male during a severe migraine attack. The visibility of the capillaries is less clear than in Fig. 2*B*.

Fig. 2*B*.—Identical field in the skin at the base of the cuticle of the same patient as shown in Fig. 2*A*. Photograph was taken ten minutes after the intravenous administration of 1.0 c.c. ergotamine tartrate (1:2,000), while the loops showed clearer visibility and the migraine attack had been alleviated subjectively.

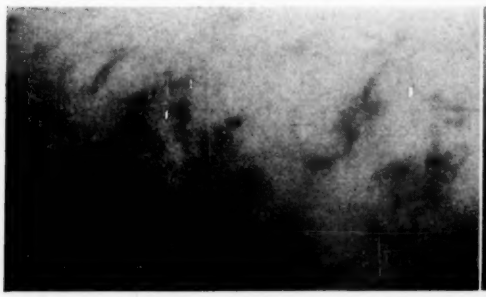

Fig. 2*C*.

Fig. 2*D*.

Fig. 2*C*.—Capillary loops in the mucous membrane of the inner surface of the lower lip, near the vermilion border, taken of the same patient as shown in Fig. 2*A* during the same migraine attack. Note the poor visibility of the capillary outlines and the similarity to the state shown in Fig. 2*A*. Compare also with Fig. 2*D*.

Fig. 2*D*.—Similar field, of the same region as shown in Fig. 2*C*. The photograph was taken fifteen minutes after the intravenous administration of 1.0 c.c. of ergotamine tartrate (1:2,000), when the vessels showed decreased "blurring" and the migraine attack was relieved.

STUDIES ON WATER DIURESIS

The visibility changes reported in the preceding sections indicated the possibility that a disturbance in the water balance existed during the migraine attack. Effort was made, therefore, to study, in migraine patients, the effect of the ingestion of 1,500 c.c. of water. Venous

pressure readings and capillary microscopy were carried out on fifteen migraine patients in twenty-nine experiments. Venous pressure was measured in all but three cases; capillary observation and photography were carried out in sixteen experiments.

Volhard and Fahr[18] have shown that the ingestion of 1,000 to 1,500 c.c. of water by a normal adult induces the output of a quantity of urine slightly in excess of the amount ingested, within four hours. A quantity of urine in excess of half of the amount ingested is excreted within the first two hours. The specific gravity usually falls as low as 1.002 in the second hour. A dry meal, given four hours after the ingestion of the fluid, is usually followed by the voiding of a small volume of urine within the next four to six hours, the specific gravity of which may reach a concentration of 1.028 to 1.032.

PROCEDURE

Since the results of the Volhard and Fahr test have been shown to be modified by renal and circulatory insufficiency, it was ascertained that these conditions did not exist in the patients tested. All the tests were begun early in the morning, after the subject had fasted for about twelve hours. The patient voided before ingesting the water. The subject remained at rest in bed throughout the test. A total of 1,500 c.c. of tap water was ingested by mouth within five to ten minutes. The volume of urine excreted and the specific gravity were measured every hour for four hours, and every other hour for another four hours after the administration of a dry meal.

Venous pressure was measured by means of the indirect method of Eyster and Hooker,[19] rather than the method of Moritz and v. Tabora,[20] because it permits frequently repeated readings, is rapid and painless, does not cause any marked interference with the circulation, and the readings compare fairly closely with those obtained by the direct method except for the effect of tissue pressure.[21] The indirect method can, however, be employed only on persons with clearly visible venous channels on the forearm or dorsum of the hand.

RESULTS

The results of twenty-nine experiments on fifteen patients are as follows:

1. Fourteen of the fifteen migraine patients showed an abnormal "excess excretion" rate within the period of the dilution experiment.* As this excess excretion subsided, a migraine attack developed in twenty-one of the twenty-nine experiments. Excess excretion was maintained throughout the concentration period† in four instances, and in none of these did a migraine attack develop. In four instances, relief of the migraine attack occurred, together with a second increase in urine flow.

*The four hours after taking 1,500 c.c. of water.
†The four hours after eating the dry meal.

2. In two cases, 0.5 mg. of ergotamine tartrate was injected intravenously at the height of the migraine attack which had developed with complete cessation of urine flow. In both instances relief set in with diuresis and profuse perspiration.

3. Small and inconstant venous pressure variations occurred in four instances; no headache developed. In fifteen instances the venous pressure dropped simultaneously with the cessation of urine flow and the development of an attack, and remained low throughout the attack (Table I).

TABLE I

SUMMARY OF VENOUS PRESSURES IN RELATION TO DEVELOPMENT OF HEADACHE AFTER FORCED FLUID INTAKE IN MIGRAINE PATIENTS

	HEADACHE DEVELOPED			HEADACHE DID NOT DEVELOP			ERGOTAMINE TARTRATE INJECTED AT HEIGHT OF HEADACHE		
No. of experiments	15			9			2		
	BEFORE FLUID INTAKE	LOWEST AFTER FLUID INTAKE	HIGHEST AFTER FLUID INTAKE	BEFORE FLUID INTAKE	LOWEST AFTER FLUID INTAKE	HIGHEST AFTER FLUID INTAKE	BEFORE FLUID INTAKE	LOWEST AFTER FLUID INTAKE	HIGHEST AFTER FLUID INTAKE
Range of venous pressure in cm. water	7-10	4-8	10-17	5-11	4-9	6-15	9-9	6-8	13-14
Average of venous pressure in cm. water	8.6	5.9	12.8	7.9	6.9	11.2	9.0	7.0	13.5

4. The majority of patients did not show blurring of the capillaries or suffer from headache before ingestion of the fluid. Although about half exhibited slight blurring of the capillaries and complained of slight headache during the period of dilution, the noticeable fact is that, during the period of concentration, half of the patients showed marked blurring of the capillaries and complained of severe headache (Table II).

TABLE II

STATE OF CAPILLARY VISIBILITY AND HEADACHE DURING THE PHASES OF THE VOLHARD AND FAHR TEST

CAPILLARY VISIBILITY AND HEADACHE	BEFORE INGESTION	DURING DILUTION	DURING CONCENTRATION	TOTAL
No blurring and no headache	8	6	0	14
Slight blurring and no headache	4	2	2	8
Slight blurring and slight headache	2	7	3	12
Slight blurring and marked headache	0	0	1	1
Marked blurring and slight headache	0	0	2	2
Marked blurring and marked headache	1	0	7	8
Total	15	15	15	

5. In one instance ergotamine tartrate was administered intravenously four hours after ingestion of water, at the height of the headache. Some blurring of the capillaries had been present from the beginning of the observation, but, after the injection, the blurring became slightly less, and varied greatly along with the occurrence of diuresis and cessation of headache (Fig. 3).

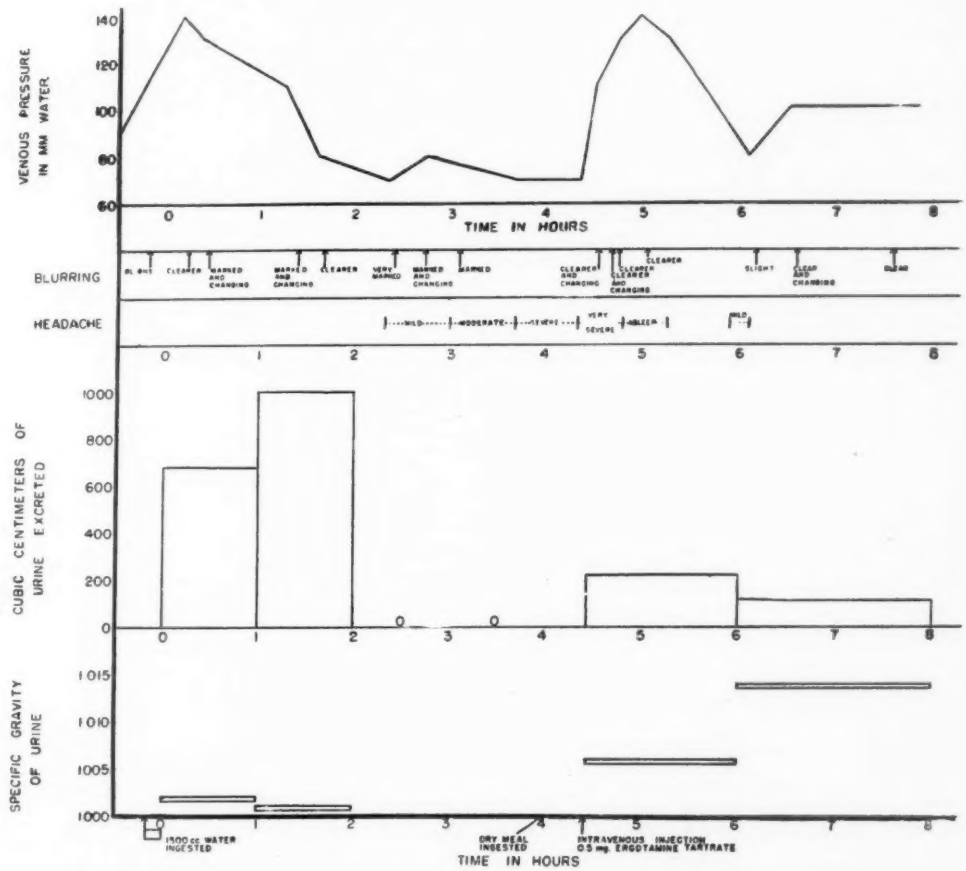

Fig. 3.

6. Only one of the fifteen patients, a woman, 18 years of age, showed an almost normal excretion curve. She was also the only one of the group whose age was under 30 years. According to her history, the migraine attacks from which she had suffered had been of infrequent occurrence and of a mild nature.

DISCUSSION

Any critical evaluation of the results of capillary microscopy and photography depends upon adoption of definite criteria for deciding

upon the limits within which a capillary blood vessel may be called normal, and upon appreciation of the sources of error and limitations of the methods. The normal capillary structure has been described by many investigators. Slight changes in diameter, a wavy course of the capillary, and irregularities in blood flow, as described by Parrisius[22] and more recently by Griffith,[23] are so common as to suggest that they belong within the range of normality.

Disturbances in the endocrine status of the subject have been reported[24-26] as giving rise to variations in the length and diameter of the visible capillary limbs, the distance between the arterial and venous channels, the pointing of the transition limb into "tent formation,"[27] the rate of blood flow, and the reactions to drugs such as epinephrine.[28, 29] Previous attempts to label definite "capillary pictures" as characteristic of certain diseases have failed largely because the microscopic changes are not usually specific for a given disease. The method is useful essentially as an additional means of study of physiologic and pathophysiologic changes in the peripheral circulation.

The significance of "blurred" capillaries in migraine needs evaluation. Explaining the observed blurring as the result of technical difficulties does not seem valid because blurring occurred so regularly in a given patient during an attack of migraine, and because the same field and mechanical setup were used. Furthermore, the change was simultaneous in skin and mucous membranes. In photographs of capillaries, blurring was difficult to interpret because the accuracy of focus could not be ascertained with sufficient reliability. The focus may change in the unanesthetized living subject during exposure of the film because of the limited fixation of the part studied. Observation is obviously superior to photography for studying changes in visibility.

Change in the state of visibility of the capillary outline was reported by Cohnheim[30] to occur in inflammation, and was believed to be related directly to swelling of the endothelial cells of the capillary walls. During wheal formation, increasing capillary indistinctness has been observed to culminate in a final capillary tamponade.[31] The experiments in diuresis also suggest that the distinctness of capillary outlines is directly related to the transudation or exchange of material through the capillary wall. Occurrence of blurring in the capillaries of the body surface does not, however, permit the assumption of similar changes in the cerebral capillaries, even though similarity in the response of the capillaries of the two regions in question has been described.[32-34]

In contrast to the changes in the state of visibility, changes in the form of the capillaries can be recorded with more accuracy. The significance of deviations in form which alter the basic characteristics of the loop is not sufficiently understood. It is difficult to state what deviations from the normal are to be considered as reactive, regressive, or the result of failure in development of capillaries. The variability

in diameter recalls the "angioneurotic diathesis" described by Parrisius[22] and Mueller.[35] It has been recently indicated by Mueller[36] that persons who have such changes in capillary form and diameter tend to have an increased susceptibility to vasomotor disturbances, allergy, and migraine.

The mechanism of the action of ergotamine tartrate is not fully understood. Our observations suggest the existence of a relationship between the fluid exchange through the capillary walls, and relief of some of the symptoms of the migraine attack by the action of ergotamine tartrate. Additional information regarding the effect of ergotamine tartrate on the capillaries in normal persons and in the interval between migraine attacks is needed.

The studies on water diuresis indicate a relationship between the water balance of the body, the state of the peripheral capillaries, and the migraine attack. Forced ingestion of water induced an excessively high rate of excretion in fourteen of fifteen migraine patients, a fact which suggests that the pre-edematous state of Volhard and Fahr[18] existed. Fremont-Smith and Merritt[37] have reported that the induction of epileptiform seizures by forced fluid intake takes place in the absence of changes in intracranial pressure. It is therefore unlikely that the development of headache after forced fluid intake in our studies was mediated by changes in intracranial pressure.

A correlation in time between urine flow and onset and alleviation of the headache was consistent in the reported experiments; cessation of urine flow coincided with the onset of headache in the twenty-one instances in which an attack developed. Further, in the two instances in which ergotamine tartrate was administered intravenously at the height of the attack, the relief of headache coincided with a dramatic resumption of diuresis.

The variations in venous pressure were not large enough to be clear in significance. The fact that venous pressure fell slightly in each instance of an induced attack of migraine may be considered as additional evidence of loss of fluid from the circulatory system into the tissues.

SUMMARY

1. An attempt was made to study changes in the capillaries of the body surface with respect to their possible relationship to the migraine attack.

2. Impaired visibility of the surface capillary outlines, or "blurring," was observed during 142 migraine attacks in 118 patients. Its possible relationship to a physiologic mechanism is discussed.

3. Changes in the visibility of the surface capillary vessels were found to follow a definite course subsequent to intravenous injections of 0.25 or 0.5 mg. ergotamine tartrate, in twenty of twenty-three instances.

4. Observations during migraine attacks induced by forced water ingestion seem to indicate a definite relationship between the fluid balance of the body, the state of the peripheral capillaries, and the migraine attack.

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THE BLOOD PRESSURE IN ESSENTIAL HYPERTENSION: EFFECT OF SEVERAL REPUTEDLY HYPOTENSIVE DRUGS

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ESSENTIAL hypertension is an extremely widespread disease. It has been estimated by one author[1] that almost a fourth of all deaths of persons more than 50 years old are directly attributable to hypertension. The leading position of cardiovascular-renal diseases in tabulations of causes of death is familiar to all. Hypertension accounts for a large percentage of these deaths. In a series of 150 cases of cardiac decompensation, Dry[2] found that in 76 per cent of cases "cardiac decompensation was on the basis of hypertension and coronary disease either independently or in association with each other. . . ." The influence of elevation of the blood pressure on life expectancy has been clearly demonstrated by Keith, Wagener, and Barker.[3] These authors found that even in the "benign" or relatively stationary types of essential hypertension, the median duration of life after the first examination is 100 months (8.3 years) for patients who have a minimal, or group I, classification. Among their patients with maximal, or group IV, hypertension, the median duration of life after the first examination was but 5.4 months. This has been confirmed by others.[4] Thus, there is an ample stimulus for search for improved treatment for this widespread disease.

In the more than forty years that have elapsed since Allbutt[5] described the syndrome of essential hypertension—indeed, in the century or more since Bright initiated interest in problems regarding high blood pressure, a successful, practical, and safe method for the routine treatment of essential hypertension has not been devised. Many drugs have been advocated for the medicinal treatment of high blood pressure. Casual perusal of a recent listing[6] of drugs and pharmaceuticals reveals almost 100 names of "hypotensive" drugs which are alleged to be of value in such treatment. In 1930, Ayman[7] found at least 200 reports of the successful treatment of essential hypertension by different drugs and methods. He pointed out that the constant employment of new drugs and the continued high mortality rate associated with essential hypertension indicate that the proper treatment is still unknown. This statement might well have been made today. In this excellent review, Ayman pointed out certain fallacies in these claims, which are involved in the interpretation of therapeutic results. (Perusal of the literature of the

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subsequent decade would suggest that these pertinent warnings have been generally disregarded.) The claim of "successful" treatment of essential hypertension often is based only on symptomatic improvement of the patient, rather than on any substantial reduction of the blood pressure. Most authors agree that the symptomatic status of the hypertensive patient has little relationship to the levels of the blood pressure.[8-11] In a further discussion on the interpretation of "relief of hypertension," Ayman[12] pointed out additional pitfalls which claim the unwary. The most important of these is the lability of the blood pressure among hypertensive persons. Wide fluctuations in blood pressure from time to time necessitate[13-16] making careful control observations to allow for appreciation of this factor in the treated patient. Otherwise, this striking instability may account for an apparent hypotensive effect. This factor also becomes an important consideration in the establishment of criteria for determination of a "hypotensive" effect.

The refractory nature of hypertension is further confirmed by the large number of medical techniques which continue to appear. It seems unlikely that all of the large number of drugs now available[6] are capable of lowering the blood pressure in hypertensive patients. It is noteworthy that when the results of "successful" treatment are analyzed to show symptomatic improvement, as separate from actual reduction in blood pressure, it becomes apparent that, although symptomatic response is relatively easily obtained, reduction of blood pressure is difficult. Sometimes it is said that symptomatic improvement is a sufficient end in itself, and that reduction in blood pressure is undesirable; and that, if this latter condition is established, the patient may suffer. It is by no means demonstrated that such a statement is true, and experienced observers[7, 17, 18] of hypertensive patients feel that, on the contrary, reduction of blood pressure is the essential aim of treatment. The fact that the symptoms of hypertension can be controlled in many ways,[7, 19, 20] and that, with excellent symptomatic control easily available, the mortality rate has not been reduced over a period of years, would lead to the conclusion that the symptoms associated with hypertension do not measure any factor contributing to death in these patients. It seems more reasonable to conclude that elevated levels of blood pressure are significant contributory factors in the established mortality rate. Indirect support of this contention is seen in the advertising appeals of manufacturers, who often make extravagant claims for the hypotensive properties of their particular remedies.

In a more recent therapeutic assay of drugs which are reputed to be effective in controlling essential hypertension, Evans and Loughnan[18] agreed that the desirable (that is, hypotensive) effect is rarely obtained, but that good symptomatic response can be obtained by the use of many drugs. In their series, placebo medication was generally as effective as any "hypotensive" drug that they used. These authors also pointed

out that many drugs are praised in the absence of controlled clinical observations. Thirty-three drugs, in all, were exhibited by them, including nitrites, iodides, bromides, barbiturates, and antispasmodic agents such as atropine and papaverine sulfate. These authors set up certain seemingly fair critical standards for judgment as to whether or not a drug is "hypotensive." Such a drug must reduce the blood pressure when it is originally elevated, must demonstrate this action consistently and in a high proportion of patients, and, last, must do this without producing symptoms of toxicity. In the present study, these have been accepted as suitable criteria for similar adjudication of the drugs concerned. At the conclusion of the aforementioned studies, Evans and Loughnan agreed that they could not approve the prescribing of any of these drugs if the object was to reduce the blood pressure!

PURPOSE OF THE PRESENT STUDY

It was the intention, in the initiation of this study, to assay the actual hypotensive effects of a number of commonly used and widely recommended drugs on patients who had a persistently elevated blood pressure. Because of previous demonstrations that symptomatic improvement is commonly obtained by many methods of treatment,[7, 19, 20] a careful attempt was made to exclude any consideration of subjective response. As stated before, it is my conviction that the mediator of the high mortality[3, 14, 17] rate of essential hypertension is the level of intra-arterial pressure itself.

METHODS OF STUDY

Patients.—The patients were selected from a group of persons who were resident in a state hospital for the insane.* This selection was made deliberately, for it was felt that such a group of patients were relatively insensitive to their immediate environment, and all were, perforce, subjected to considerable routine in their daily lives. Also, few, if any, of these patients complained of symptoms of elevated blood pressure, although some were rather ill from the consequences of it. The patients included those who had schizophrenia, manic depressive psychosis, depression, arteriosclerosis of the vessels of the central nervous system, with attending dementia, and some other types of committable mental disturbances. All patients were hypertensive males, with ages ranging from 38 to 70 years. All patients ate the same meals, and each subgroup included those in rather close confinement to the wards, and those allowed more freedom, who carried on simple occupations around the institution. In general, it was a group of patients subjected to much the same environment and routine.

Procedure.—Most of the patients were not told that they were receiving medication, or that they suffered from high blood pressure. A few who exhibited curiosity concerning their pills were told that it was "good for them," and a small number of alert and interested patients were told that they had some slight abnormalities of blood pressure for which they were receiving medication. Last, a small number of institutional employees were treated gratuitously, with full understanding of their abnormal state and the purpose of the study. It was felt that these latter groups would act as controls for evaluation of certain obvious factors.

*We wish to extend our thanks to Dr. B. F. Smith, superintendent, Rochester State Hospital, for his generosity and cooperation in this study.

All persons reported on in this study were subjected to minimal examinations for the purpose of ruling out certain etiological factors which might cause hypertension. Examination of the optic fundi and urinalysis were carried out, and roentgenograms of the thorax were made, in addition to careful physical examination. When observations were made that were suggestive of glomerulonephritis or other significant renal disease, coarctation of the aorta, increased intracranial pressure, or certain endocrine disturbances, including hyperthyroidism, pituitary basophilism, and adrenal tumor,[21] the patients concerned were omitted from this study. Arteriosclerosis and obesity were not disqualifying for our purposes. Admittedly, some of the aforementioned disturbances may have been present in spite of care taken to exclude them, but it is not likely that the majority of the patients had any cause for elevated blood pressure other than essential hypertension. It was not felt that an abnormal psychic state should be disqualifying, because hypertension is not characteristically observed in the presence of psychoses, and the large majority of the patients of this institution had normal blood pressure. No patient with the clinical or ocular criteria[3, 22] of "malignant" hypertension was included in this series.

This large group of selected patients was classified into subgroups, referred to by number in Tables I, II, III, IV, V, VI, VII, and VIII. These subgroups were composed of up to ten men, and an attempt was made to include an approximately equal number in each subgroup. Attention was paid to age, occupation, and physical habitus. No deliberate attempt was made to select the subgroups on a basis of the value for the blood pressure or the grouping of the vascular lesion,[3] because it was soon apparent that each group was composed of representative patients. Members of each group were given one drug in the dosage recommended by the manufacturer, or other advocate of the product, or in a dosage even exceeding the suggested optimum. The medications were given before meals as a matter of routine. Patients who for reasons of temperament or delusion refused medication for more than one day, or who were detected in attempts to deceive, were eliminated from the study, and new patients were substituted for them. All drugs were ingested by patients under the supervision of experienced attendants. All patients who received other medications independent of this study were omitted from consideration if those medications included sedative agents, iodine-containing substances, digitalis, or other drugs that might affect the blood pressure. Actually, the only other medicines given to these patients during the period of this study included mineral oil, milk of magnesia, insulin (three patients), skin disinfectants, and antipruritic lotions.

Measurements of the blood pressure were made at least three times daily, i.e., before breakfast and lunch, and after supper. With certain few exceptions, all measurements were made by one examiner, and in accordance with the suggestions of the joint British-American Committee[23] for standardization of methods of taking blood pressure. In a few instances in which this was not done, a dispensary attendant, carefully trained according to the aforementioned technique, took the readings. These instances were so few that they did not significantly alter the results. In all cases the daily maximal and minimal systolic and diastolic pressures were recorded, so that in the tables only two daily readings are presented. Among all patients a period of seven to ten days in which medication was not given was devoted to measuring the blood pressure and its fluctuations.

The study period included the seven- to ten-day pretreatment period, and at least thirty days of continuous observation while the patients were under treatment. In almost all cases a further observational period of seven to ten days, after discontinuance of all treatment, was allowed for the detection of any changes in blood pressure that might conceivably occur as "delayed" responses. Thus, it seemed reasonable that within thirty to forty days any hypotensive effects should become manifest.

Certain reasonable criteria had been decided upon, previous to the study, for definition of a hypotensive effect. These had been used by previous investigators.[12, 18] Prior to, and during, this inquiry a moderately skeptical attitude, rather than an entirely open mind, possessed the author, but perusal of the results will soon demonstrate that any misgivings on this score can be set aside.

DRUGS

The drugs used in this study usually were selected with a view of obtaining at least one representative of each of the currently highly popular types of chemicals used in attempts at regulation of blood pressure. One outstanding omission was potassium thiocyanate, for the technical difficulty of using this drug in such a study is apparent. Furthermore, most authors[24, 25] are in agreement as to the status of this drug, for many careful and adequate studies of its effects have been made. Some drugs were selected because they had been widely advertised and remarkable claims had been made for them. All drugs used were purchased from ordinary sources.

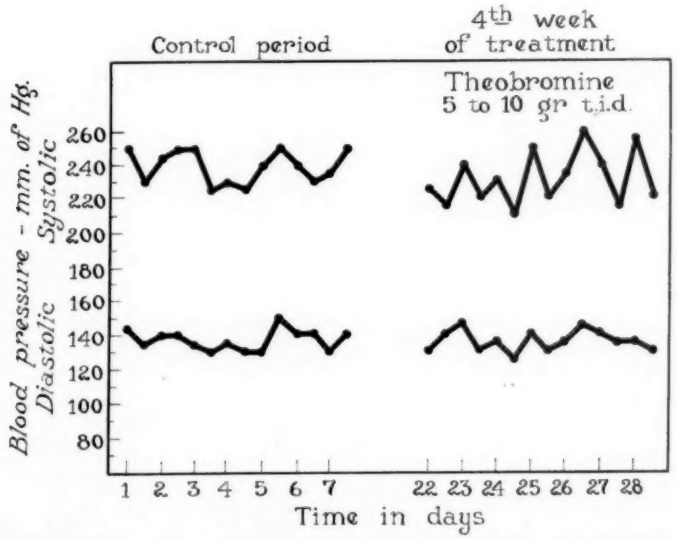

Fig. 1.—Daily values for diastolic and systolic blood pressure in control period and during the fourth week of treatment with theobromine, in a typical case.

TABLE I

RESULTS OF TREATMENT WITH THEOBROMINE, AS INDICATED BY AVERAGE SYSTOLIC AND DIASTOLIC BLOOD PRESSURES

PATIENT	PRESSURES BEFORE TREATMENT	PRESSURES AFTER GIVEN WEEK OF TREATMENT 1	2	3	4	PRESSURES AFTER TREATMENT
1	182/125	185/130	182/126	175/122	188/126	186/129
2	165/116	165/116	166/112	163/112	159/109	168/113
3	157/111	158/111	165/119	170/121	186/121	179/123
4	239/136	221/134	225/132	226/134	232/136	239/135
5	183/106	170/104	175/108	181/107	178/111	183/112
6	186/117	178/109	175/111	184/114	179/116	180/116
7	179/110	178/102	171/100	168/102	168/ 97	Incomplete
8	203/113	194/115	189/118	188/118	187/121	193/120
9	188/101	187/112	187/110	189/110	184/109	Incomplete
10	212/123	203/120	202/123	206/122	205/122	Incomplete

The methylated xanthine derivatives enjoy widespread favor and, in various forms and combinations, constituted the largest single group of drugs studied. Cushny[26] stated that "All members of the caffeine series have been shown in animals to dilate the coronary vessels, but how far these results can be carried over to man is still an open question." In this group, theobromine, a prepared combination of theobromine and phenobarbital sodium (theominal), a proprietary arterial antispasmodic agent (iocapral), and theophylline with ethylene diamine (aminophylline) were tried.

Theobromine.—Theobromine (3, 7 dimethylxanthine) was given three times daily, with meals, in capsules of 5 grains (0.3 Gm.) each. Patients numbered 1 through 10 (Table I) received this drug, and, after two weeks of consecutive use of it, the dose was doubled (Fig. 1); that is, for the second two weeks of consecutive use, the dose was 10 grains (0.65 Gm.) three times daily.

Theobromine and Phenobarbital Sodium.—Theominal, a proprietary drug, was administered to patients numbered 11 through 20 (Table II). This preparation contains, according to the manufacturer's statement, 5 grains (0.3 Gm.) of theobromine

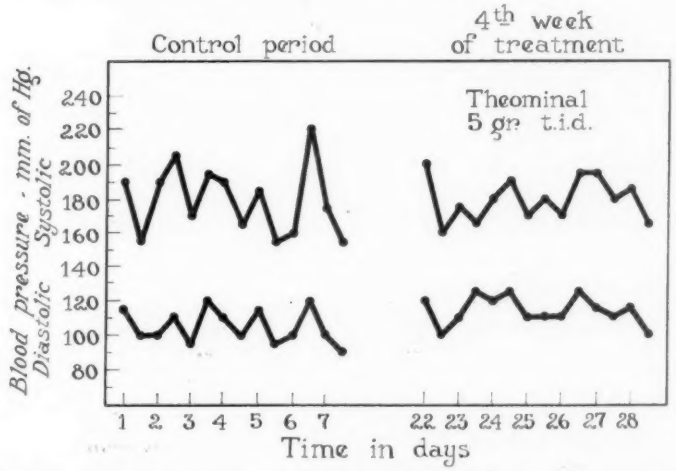

Fig. 2.—Daily values for diastolic and systolic blood pressure in control period and during the fourth week of treatment with theominal, in a typical case.

TABLE II

RESULTS OF TREATMENT WITH THEOMINAL, AS INDICATED BY AVERAGE SYSTOLIC AND DIASTOLIC BLOOD PRESSURES

PATIENT	PRESSURES BEFORE TREATMENT	PRESSURES AFTER GIVEN WEEK OF TREATMENT 1	2	3	4	PRESSURES AFTER TREATMENT
11	176/115	176/117	176/118	176/115	180/117	185/115
12	180/119	191/125	180/116	174/114	179/119	180/121
13	178/104	165/104	169/104	183/111	177/113	Incomplete
14	191/106	194/116	197/124	196/115	196/124	Incomplete
15	181/100	179/ 99	179/ 98	194/103	Refused further treatment	
16	186/114	180/111	186/112	185/114	183/118	Incomplete
17	183/103	202/110	194/112	184/115	Refused further treatment	
18	184/108	169/104	168/ 95	175/106	184/109	Incomplete
19	170/ 99	174/101	172/100	172/105	171/104	189/107
20	203/118	192/117	199/118	197/121	Died suddenly	

and a half-grain of phenobarbital sodium (luminal) to the tablet. This was given in the recommended dose of one tablet three times daily. For seven of these ten patients four consecutive weeks of treatment were carried out (Fig. 2), whereas, for three, shorter periods were occasioned by unanticipated events, as set forth in Table II.

Proprietary Arterial Antispasmodic Agent.—Iocapral, also a proprietary remedy, was administered to only five patients for a four-week period (Fig. 3). The patients were numbered 21 through 25 (Table III). This preparation, according to the manufacturer's statement, contains 5 grains (0.3 Gm.) of theobromine, two-thirds of

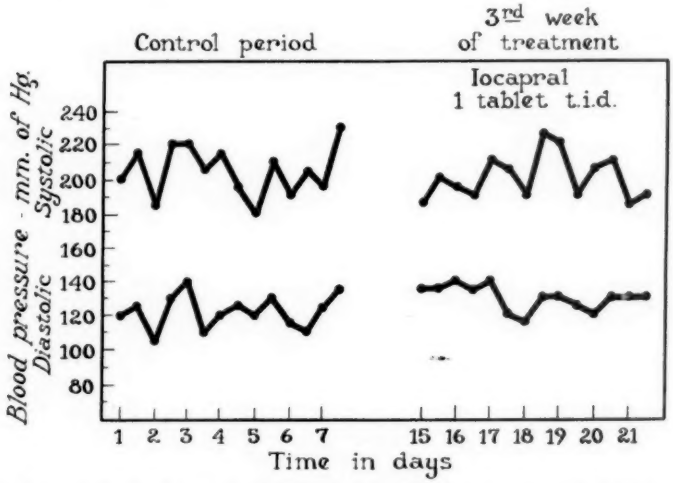

Fig. 3.—Daily values for diastolic and systolic blood pressure in control period and during the third week of treatment with iocapral, in a typical case.

TABLE III

RESULTS OF TREATMENT WITH IOCAPRAL, AS INDICATED BY AVERAGE SYSTOLIC AND DIASTOLIC BLOOD PRESSURES

PATIENT	PRESSURES BEFORE TREATMENT	PRESSURES AFTER GIVEN WEEK OF TREATMENT 1	2	3	4	PRESSURES AFTER TREATMENT
21	181/116	179/115	187/116	179/122	184/120	185/116
22	174/104	167/104	171/106	169/109	178/108	172/105
23	178/116	182/118	184/119	179/120	183/120	182/117
24	170/118	173/122	170/122	172/119	177/126	177/123
25	205/123	210/135	199/134	199/129	203/125	207/125

TABLE IV

RESULTS OF TREATMENT WITH AMINOPHYLLINE, AS INDICATED BY AVERAGE SYSTOLIC AND DIASTOLIC BLOOD PRESSURES

PATIENT	PRESSURES BEFORE TREATMENT	PRESSURES AFTER GIVEN WEEK OF TREATMENT 1	2	3	4	PRESSURES AFTER TREATMENT
26	165/101	171/107	180/107	190/113	172/105	181/110
27	224/136	234/135	228/138	229/134	228/136	237/137
28	175/112	169/112	179/115	177/112	173/115	180/119
29	181/111	180/113	180/116	184/117	187/113	194/112
30	205/121	204/125	204/122	202/120	199/123	199/124

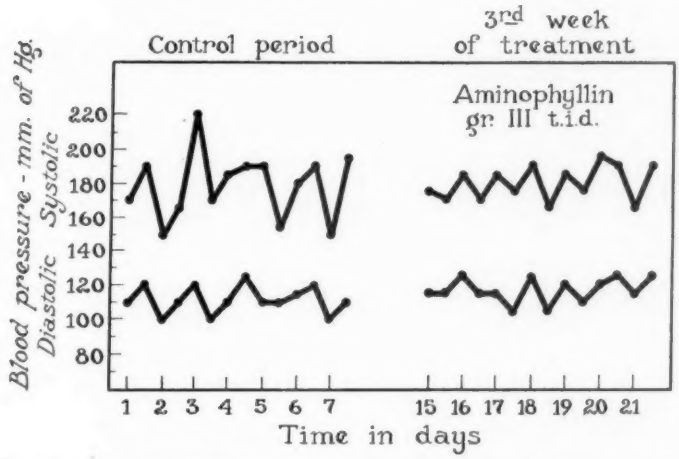

Fig. 4.—Daily values for diastolic and systolic blood pressure in control period and during the third week of treatment with aminophylline, in a typical case.

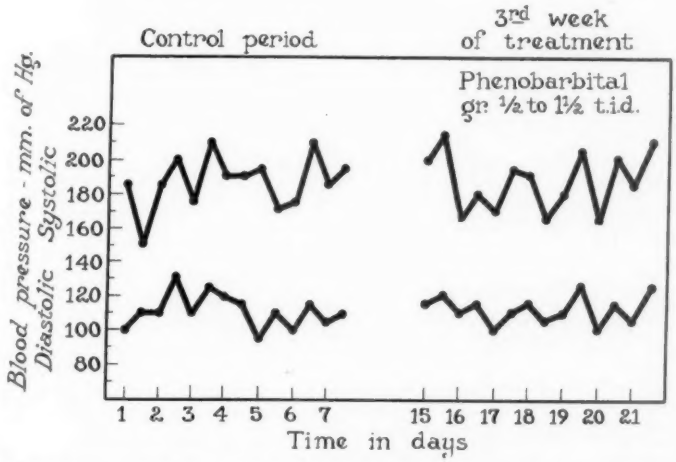

Fig. 5.—Daily values for diastolic and systolic blood pressure in control period and during the third week of treatment with phenobarbital, in a typical case.

TABLE V

RESULTS OF TREATMENT WITH PHENOBARBITAL, AS INDICATED BY AVERAGE SYSTOLIC AND DIASTOLIC BLOOD PRESSURES

PATIENT	PRESSURES BEFORE TREATMENT	PRESSURES AFTER GIVEN WEEK OF TREATMENT				PRESSURES AFTER TREATMENT
		1	2	3	4	
31	146/ 95	144/ 94	149/ 98	153/ 99	149/103	148/104
32	157/102	144/102	152/104	144/ 96	152/105	146/106
33	184/112	193/115	194/115	189/118	190/119	186/120
34	168/103	157/ 98	149/ 93	148/ 94	141/100	142/104
35	211/ 96	209/100	208/111	192/108	209/111	215/115
36	186/112	182/110	191/112	185/111	186/113	182/114
37	187/121	180/122	174/122	176/119	181/121	183/122

a grain of mebaral (a brand of mephobarbital, or N-methylethylphenylbarbituric acid), and 2 grains (0.13 Gm.) of calcium iodide ditriethanelamine in each tablet. One tablet was administered three times daily throughout the usual thirty-day period.

Theophylline With Ethylene Diamine.—Aminophylline, a brand of theophylline with ethylene diamine, containing from 70 to 80 per cent of anhydrous theophylline (1, 3-dimethylxanthine), was the last of this group of drugs used. This also was administered to five patients, numbered 26 through 30 (Table IV), for the usual period of thirty days, in a dosage of 3 grains (0.2 Gm.) three times daily (Fig. 4).

Phenobarbital.—Phenobarbital, alone, in varying dosages, was given to seven patients for a minimum of four consecutive weeks. These records are numbered 31 through 37 (Table V) (Fig. 5).

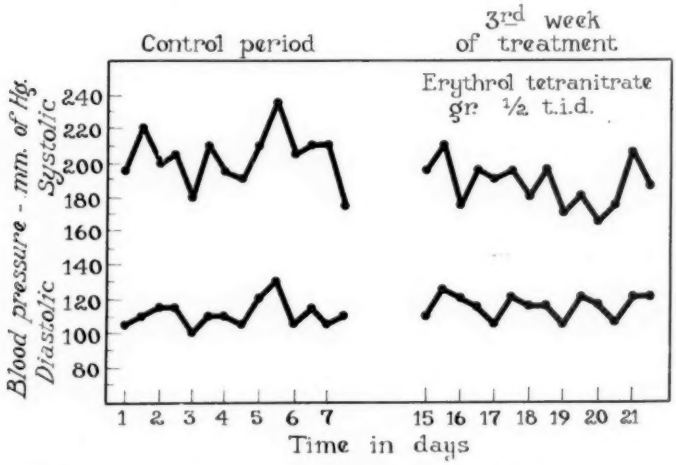

Fig. 6.—Daily values for diastolic and systolic blood pressure in control period and during the third week of treatment with erythrol tetranitrate, in a typical case.

TABLE VI

RESULTS OF TREATMENT WITH ERYTHROL TETRANITRATE, AS INDICATED BY AVERAGE SYSTOLIC AND DIASTOLIC BLOOD PRESSURES

PATIENT	PRESSURES BEFORE TREATMENT	PRESSURES AFTER GIVEN WEEK OF TREATMENT 1	2	3	4	PRESSURES AFTER TREATMENT
38	202/130	205/129	212/131	199/129	200/130	203/130
39	164/105	161/105	162/107	165/107	164/111	170/110
40	211/111	199/111	206/115	195/116	199/116	189/122
41	167/116	164/110	162/109	174/111	169/110	168/110
42	233/135	239/138	239/138	233/135	240/138	232/140

The nitrites (and nitrates) have been known as vasodilators for many years. Brunton[27] wrote, in 1897, that inhalation of amyl nitrite causes "a very great fall of the blood pressure." Since that time, extensive search has been made for a nitrite or nitrate which would be relatively nontoxic and yet cause prolonged vasodilatation. It was not possible in this study to use all of the organic and inorganic nitrites and nitrates that have been introduced for the management of hypertension. A representative was chosen, after the recommendations of Goodman and Gilman.[28]

Erythrol Tetranitrate.—Erythrol tetranitrate ($C_4H_6[NO_3]_4$), the nitration product of erythrol (tetrahydroxybutane), was administered for the usual period in a dosage

of a half-grain (0.032 Gm.) three times daily (Fig. 6) to patients numbered 38 through 42 (Table VI).

A Proprietary Hypotensive Agent.—A proprietary remedy known as hepvisc, of complex and uncertain composition, was administered (Fig. 7) to eleven patients, numbered 43 through 53 (Table VII). Of these eleven patients, nine took this medicine for four weeks and two took it for shorter periods. The scheme of administration, as recommended by the manufacturer, is "one to two tablets three times daily, one-half hour before meals. Best results are obtained when medication is given in courses of two to three weeks, allowing a week's rest interval between courses." This advice was carefully followed. The manufacturer claims that this tablet is "a synergistic combination of *Viscum album* (European Mistletoe), and hepatic and insulin-free pancreatic extracts. It is much to be preferred to the nitrites and other depressing drugs." The advertisements also state that hepvisc is "for prolonged relief of blood pressure." The latter statement seems somewhat ambiguous.

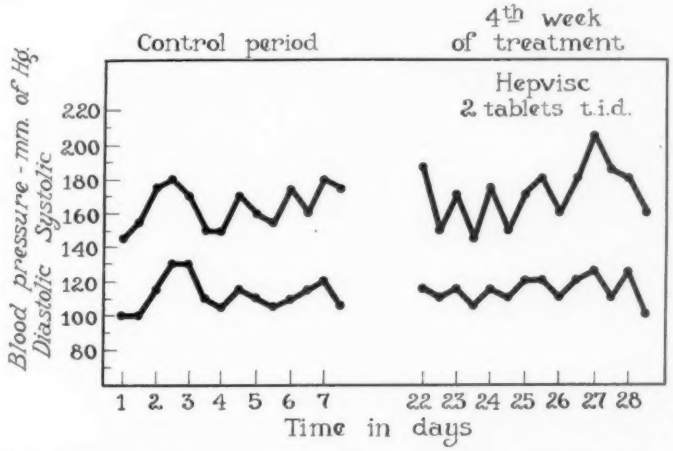

Fig. 7.—Daily values for diastolic and systolic blood pressure in control period and during the fourth week of treatment with hepvisc, in a typical case.

TABLE VII

RESULTS OF TREATMENT WITH HEPVISC, AS INDICATED BY AVERAGE SYSTOLIC AND DIASTOLIC BLOOD PRESSURES

PATIENT	PRESSURES BEFORE TREATMENT	PRESSURES AFTER GIVEN WEEK OF TREATMENT 1	2	3	4	PRESSURES AFTER TREATMENT
43	164/112	160/109	163/114	160/111	174/114	165/113
44	166/103	156/ 99	157/101	158/103	166/109	161/105
45	198/118	202/116	220/124	216/120	Fractured hip; bronchopneumonia	
46	165/106	172/116	169/109	167/106	167/108	159/103
47	158/105	158/101	161/104	168/110	165/108	164/106
48	215/137	204/131	190/128*	180/121*	184/119*	185/120*
49	184/125	175/123	178/121	178/121	183/125	178/123
50	166/111	188/118	183/119	187/119	188/121	180/120
51	142/100	143/ 96	148/101	145/100	145/ 99	146/100
52	185/118	188/120	192/126	191/121	197/120	191/124
53	184/109	184/109	190/113	181/110	189/111	189/117

*Rest in bed.

A Proprietary Vasodilator.—Another proprietary remedy, known as allimin, has been widely circulated among the profession. It was given (Fig. 8) to ten patients (54 to 63) for four consecutive weeks (Table VIII). This preparation is stated to be "a synergized combination, each tablet containing four and three-fourths grain garlic concentrate and two and three-eighths grain parsley concentrate with excipients and coating." Physicians are directed to give (average dose) two tablets with water, three times daily after meals for three consecutive days, omitting its use on the fourth day, and repeating this procedure indefinitely. The active principle, if any, would seem to be allyl sulfide (oil of garlic). This remedy is said by the manufacturer to produce a "systolic and diastolic drop in hypertensives," demonstrated clinically. It is also claimed to have "an antiputrefactive action in the gut—a significant collateral action in many cases of hypertension." The latter is a statement that seems hardly justified.

This list of drugs is not an imposing one when it is considered that more than 100 drugs are currently recommended as "hypotensive" agents.[6] However, the list includes representatives of many large groups of drugs which are chemically related.

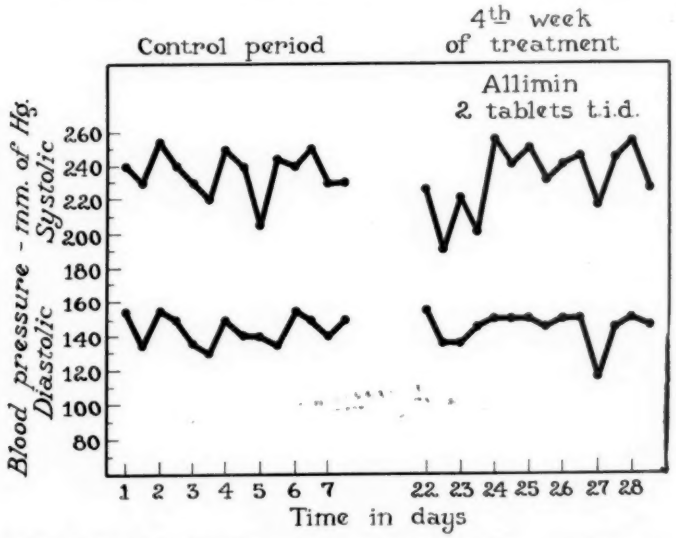

Fig. 8.—Daily values for diastolic and systolic blood pressure in control period and during the fourth week of treatment with allimin, in a typical case.

TABLE VIII

RESULTS OF TREATMENT WITH ALLIMIN, AS INDICATED BY AVERAGE SYSTOLIC AND DIASTOLIC BLOOD PRESSURES

PATIENT	PRESSURES BEFORE TREATMENT	PRESSURES AFTER GIVEN WEEK OF TREATMENT 1	2	3	4	PRESSURES AFTER TREATMENT
54	237/142	227/143	226/144	221/147	237/145	228/142
55	169/106	171/106	185/118	185/114	186/117	180/110
56	238/135	238/133	242/134	243/132	248/138	239/136
57	157/ 93	156/ 99	163/ 96	162/ 96	158/ 99	161/ 98
58	206/101	204/ 99	220/104	215/105	223/104	218/102
59	173/ 98	155/ 92	170/110	177/105	174/102	169/101
60	191/121	186/121	196/118	201/122	203/130	194/121
61	210/120	201/116	204/122	209/122	207/121	206/119
62	199/123	191/119	204/121	192/121	194/125	193/126
63	178/114	172/114	178/115	180/120	186/119	184/120

RESULTS

The results of this study, to even the most optimistic observer, are uniformly disappointing. In no single case was a sustained, significant[12] reduction in blood pressure seen. The appended tables, in which blood pressures are recorded as taken, bear evidence that no drug among those studied had any hypotensive effect when it was administered in the stated dosage for long periods. It is not likely, in view of the experiences of others,[7, 17, 18] plus the information gained in this study, that any of the groups of drugs represented by the selected examples referred to herein are likely to be any more effective.

CONCLUSIONS

On the basis of this study, it may be reasonably concluded that certain drugs, meaning those referred to herein and others similar to them, when administered continuously in optimal dosage for periods of thirty days, do not possess any significant hypotensive effect upon the blood pressure of hypertensive patients. Furthermore, the observer is strongly inclined to question the effectiveness of chemically similar drugs, of which the chosen preparations may be considered representative samples.

The author agrees with other workers[18] that the prescribing of these drugs is not to be recommended if the purpose of such prescription is to reduce the blood pressure of hypertensive patients.

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THE NORMAL BLOOD PRESSURE IN THE LOWER EXTREMITY

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INTRODUCTION

THE auscultatory (indirect) method of estimating arterial blood pressure in the arms is widely employed. Normal standards, based on figures obtained with this technique in large numbers of subjects, are already well established. So far as the authors are aware, however, similar data for the lower extremities of man are not yet available, even though the blood pressure in the thigh has been the subject of attention in cases of aortic insufficiency and coarctation of the aorta. The purpose of this preliminary report is an attempt, from a study of 500 normal soldiers, to supply this information, due consideration being given to certain modifying factors.

METHOD

The subjects used in this study were members of the United States Army Air Forces; therefore, only males were included. Their ages ranged from 18 to 35 years. They were presumed to have normal cardiovascular systems, as judged by physical, fluoroscopic, and ophthalmoscopic examination. No special selection was attempted, other than to exclude those whose blood pressure in the arm exceeded 140 mm. of Hg, systolic, or 90 mm., diastolic, or whose heart rate was over 90 beats per minute. The subjects assembled in a quiet, warm ward and remained unclothed in the supine position for at least thirty minutes prior to the measurement of the arterial blood pressure. External disturbing stimuli, apprehensiveness, and chilling were eliminated as much as possible. The environment was kept quiet, restful, and conducive to complete relaxation, as evidenced by the fact that many soldiers fell asleep. During this rest period the eye grounds and heart were examined and the temperature was taken orally. The circumference of the arm midway between the shoulder and elbow, and that of the thigh, four inches above the upper edge of the patella, were then measured by a steel tape. After the men rested for one-half hour, the pulse rate and blood pressure were recorded. The height and weight with the subjects unclothed were obtained at the conclusion of the session.

The technique and precautions recommended by the American Heart Association[1] for the estimation of the arterial blood pressure were followed with certain exceptions. As suggested, the diastolic level in the arm was recorded at the beginning of the fourth phase (muffling of the Korotkov sounds); however, in the lower extremity, since the fourth phase is inconstant, the diastolic pressure was considered to correspond

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to the point at which the sounds were no longer audible.* Also, it was found more expedient to measure the pressure in the thigh with the subject in the supine, rather than in the prone, position. One other deviation from the recommended procedure was the use of a standard-width cuff in the lower extremity instead of a wider cuff. In the arm, the bag portion of the cuff was placed over the brachial artery with the lower edge about one inch above the antecubital space, whereas, in the thigh, it was placed over the popliteal artery with the midportion of the cuff four inches above the upper edge of the patella. The blood pressure was estimated by the authors as simultaneously as possible in homolateral extremities, care being taken that the limbs were relaxed, extended, and approximately at heart level. The average of three closely agreeing measurements (one of which was checked by both observers),† taken successively and interrupted by complete deflation of the cuff, was the figure used in this study.

APPARATUS

Two standard aneroid sphygmomanometers, which were checked against each other and against a mercury manometer, were used in this study. Standard-sized cuffs, 22 inches (55.9 cm.) in length, containing a rubber bag 5½ inches (14 cm.) in width and 9 inches (22.9 cm.) in length, were employed. The cuffs were fitted with metal ribs and a locking device which prevented bulging or slipping of the inflated portion of the bag. This was particularly useful for the successful application of the cuff to the thigh. Occasionally, a thigh was too large to be inclosed in the standard-length cuff, in which case a longer cuff, measuring 29 inches (73.7 cm.) in length, was necessary.‡ The size of the rubber bag in this longer cuff was the same as that in the standard one. For ausculting the Korotkov sounds, ordinary stethoscopes with diaphragm-type chest pieces of approximately the same size were used in both the antecubital and popliteal spaces.

RESULTS

Blood Pressure Range.—In normal adult males between the ages of 18 and 35 years, the blood pressure in the lower part of the thigh, as measured at rest by the standard auscultatory method, ranged from 110 mm. to 230 mm. of Hg (average, 154.8 mm.) systolic, and from 60 mm. to 150 mm. (average, 91.9 mm.), diastolic. The blood pressure in the arm for the same group varied from 90 mm. to 140 mm., systolic, and 50 mm. to 90 mm., diastolic, with an average of 118.3 mm. and 70.6 mm., respectively. The difference between the average arm and thigh blood pressures was 36.5 mm., systolic, and 21.4 mm., diastolic. The average pulse pressure in the thigh was 62.9 mm., and, in the arm, 47.7 mm. In all cases the systolic pressure in the thigh exceeded the corresponding pressure in the arm. The diastolic pressure in the thigh either equalled or exceeded that in the arm; in no instance was it less.

*The auditory perception of the authors was checked with an audiometer, and it was found in both instances to be normal in the frequency range from 128 to 9,747 cycles per minute.

†Shock and Ogden[2] have shown by statistical analysis that such a procedure reduces any significant error to a minimum.

‡A cuff with an extension to fit exceptionally large thighs was supplied through the courtesy of the Taylor Instrument Company, Rochester, New York.

The pulse pressure in the thigh in different subjects with similar systolic pressures was rarely identical. No consistent quantitative correlation existed between the systolic and diastolic levels in the arm and the thigh.

Fig. 1 shows that the most frequent (31.2 per cent) systolic pressure readings in the thigh were between 140 and 150 mm. of Hg. In 454 soldiers (90.8 per cent) the range was from 125 mm. to 180 mm. The most frequent (35.8 per cent) diastolic pressure readings in the thigh were between 85 mm. and 90 mm. Hg. In 444 soldiers (88.8 per cent) the range was from 75 mm. to 110 mm.

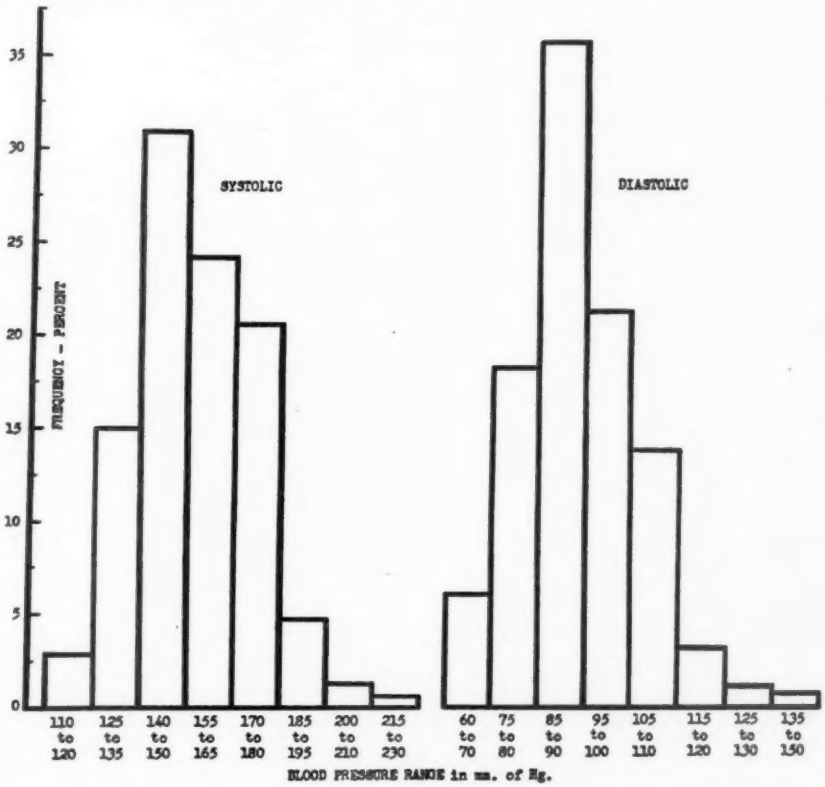

Fig. 1.—The frequency distribution of systolic and diastolic blood pressure readings obtained from the thighs of 500 normal soldiers by the auscultatory (indirect) method.

Height.—Within this group, height (66 to 78 inches) did not significantly influence the average systolic and diastolic blood pressure in the thigh.

Age.—Although age does not appear to be a modifying factor, the limited age range in this group (18 to 35 years) does not warrant any conclusions.

Sex.—Inasmuch as only male subjects were employed in this study, the influence of sex cannot be stated.

TABLE I

RELATIONSHIP OF INCREASING PULSE RATES TO AVERAGE BLOOD PRESSURE IN THE ARM AND THIGH
(The Figures in Parentheses Indicate the Range of Pressure)

PULSE RATE PER MINUTE	THIGH SYSTOLIC (MM. HG)	THIGH DIASTOLIC (MM. HG)	ARM SYSTOLIC (MM. HG)	ARM DIASTOLIC (MM. HG)	NUMBER OF CASES
51-60	151.5 (120-190)	90.5 (70-130)	115 (90-140)	70 (60-90)	62
61-70	154.1 (110-220)	92 (60-140)	115.6 (90-140)	70.8 (55-90)	151
71-80	155 (110-210)	91.7 (60-150)	118.6 (95-140)	70 (50-90)	211
81-90	159.6 (125-220)	93 (75-125)	124 (100-140)	72.7 (55-90)	76

TABLE II

RELATIONSHIP OF WEIGHT TO AVERAGE BLOOD PRESSURE IN THE ARM AND THIGH
(The Figures in Parentheses Indicate the Range of Pressure)

WEIGHT IN POUNDS	THIGH SYSTOLIC (MM. HG)	THIGH DIASTOLIC (MM. HG)	ARM SYSTOLIC (MM. HG)	ARM DIASTOLIC (MM. HG)	NUMBER OF CASES
100-140	145.4 (110-185)	85.8 (60-115)	114.8 (90-140)	69.7 (50-85)	117
141-160	150.9 (110-210)	89.6 (60-130)	116.9 (90-140)	69.4 (50-90)	190
161-180	161.5 (130-205)	96.9 (80-150)	120.9 (100-140)	71.0 (55-85)	138
181-220	169.2 (115-230)	103.7 (75-140)	121.4 (100-140)	73.0 (50-90)	55

Pulse Rate.—Table I shows that, in the pulse range from 51 to 90 beats per minute, there was a slight influence of pulse rate upon the level of the average systolic, but not upon the average diastolic, pressure. With the faster pulse rates, the systolic pressure in both the arm and thigh tended to be higher, and the greater change in this direction was in the thigh. These figures are not statistically significant.

Weight.—Table II shows that, in the weight range from 100 to 220 pounds, there was a direct relationship between the weight of the subject and the height of the systolic and diastolic pressure. This correlation existed in both the arm and the thigh, but in the lower extremity the increase in blood pressure with increase in weight was more evident. The statistical stability test shows that the sampling is adequate except for those who weighed from 181 to 220 pounds.

Circumference of Extremity.—Fig. 2, plotted from the average systolic and diastolic blood pressure readings in both the upper and lower extremities, shows, in general, that the pressure increment in the heavier subjects is dependent on the thickness of the limb. This is most evident in the highest circumference ranges of the thigh. In limbs with similar degrees of soft tissue mass (about 13 inches in circumference), the pressure in the thigh was higher by 25 mm., systolic, and 15 mm., diastolic, than in the arm.

Fig. 3 shows that the greater the average difference in circumference between the thigh and arm, the greater is the average difference between the thigh and arm blood pressure, both systolic and diastolic. The pulse rate values are almost identical in each group, which excludes tachycardia as a causative factor.

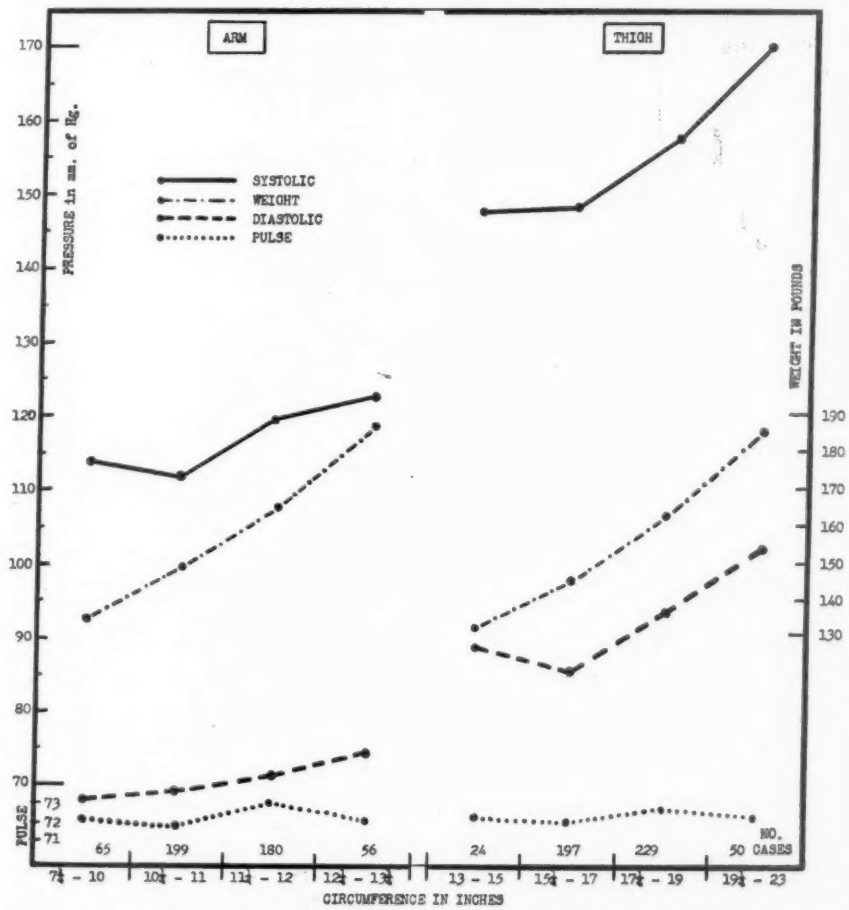

Fig. 2.—The relationship of blood pressure and weight to the circumference of the arm and thigh. The average pulse rate is also shown.

DISCUSSION

Physiologically, the height of the systolic blood pressure in the aorta and its tributaries is dependent on various factors. One of these is the conversion into lateral pressure of the kinetic energy* derived from each systolic discharge of the left ventricle. Since kinetic energy is represented by one-half of the product of the mass and the square of the velocity, the longer the blood vessel (within certain limits), the

*Bernoulli's theorem states that, except for loss by friction, the sum of the potential energy, pressure energy, and kinetic energy will always remain constant.

greater the blood mass, and, presumably, the greater the kinetic energy. This transformation of kinetic energy may be unequal in the various portions of the arterial tree, and, as has been suggested, would be greater in the femoral and popliteal vessels than in other arteries because the former represent an almost direct continuation of the large system consisting of the aorta and common iliacs with their large mass of blood.[3]

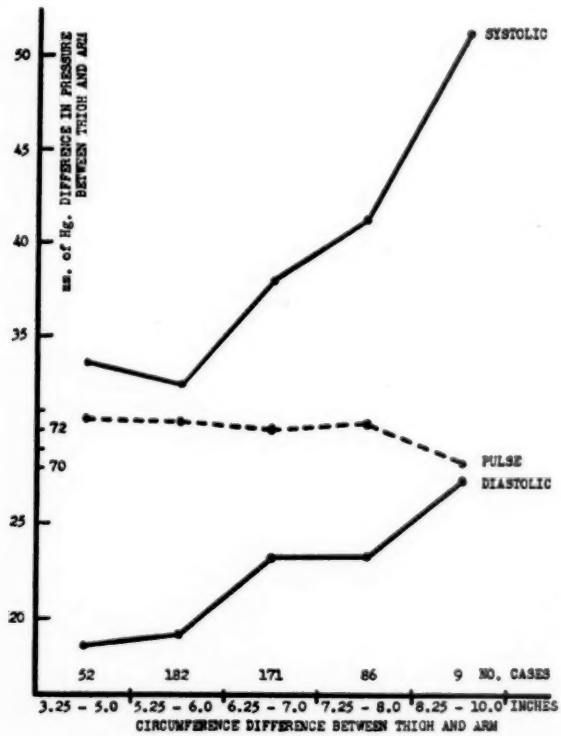

Fig. 3.—The relationship of the circumference difference to the blood pressure difference between the arm and thigh. The average pulse rate is also shown.

Hamilton and Dow[16] studied arterial pressure curves taken at different distances from the aortic arch in dogs. They showed that the peak systolic pressure increases progressively in passing down the aortic-femoral system. This they attribute to the superposition of a standing reflected wave, presumably arising from leg vessels near the knee. Thus, with the subject in the horizontal position to eliminate hydrostatic effects, it is to be expected that the systolic pressure in the thigh will exceed that in the arm. This view is supported by the observations of Burdick, et al.,[5] who employed a special photographic recording device for registration of the blood pressure in five normal adults, and concluded that the systolic pressure in the thigh is constantly higher than in the arm, and that the difference is commonly 20 to 40 mm. Hg. The present study, based on blood pressure estimations with the standard

auscultatory method on 500 normal men, indicates that, in the thigh, the average systolic and diastolic pressures are, respectively, 36.5 mm. and 21.3 mm. higher than in the arm. Therefore, the statement of Norris, et al.,[4] that "under normal conditions the systolic pressures in the arm and leg of an individual lying quietly in a horizontal position are equal" seems to be erroneous.

The weight of the subject apparently exerts a modifying influence upon the blood pressure, for higher pressures are present in the heavier subjects (Table II, Fig. 2). This observation is in agreement with the data accumulated by various investigators[6-10] concerning the relationship of obesity to the brachial blood pressure. This suggests that the soft tissue mass in a limb may, for technical reasons, affect the estimation of the blood pressure. Although others have arrived at such a conclusion by comparing the blood pressure estimations in an atrophied arm and its normal mate,[11, 12] by a comparison of intra-arterial and indirect measurements of the pressure in the same limb simultaneously,[13, 14] and by a theoretical consideration of the compressing properties of an inflated pneumatic cuff around a heavy arm,[15] none has attempted to prove this in a large series by correlating the blood pressure in a limb with the circumference. It will be seen from this study (Figs. 2 and 3) that a direct relationship exists between the circumference of the upper and lower limbs and the blood pressures as measured in them by the auscultatory method. This correlation is not invalidated by the fact that, in similar circumference groups (about 13 inches), the average systolic pressure in the thigh is about 25 mm. higher than that in the homolateral arm (Fig. 2), for this is a normal difference.[5] No quantitative relationship between the thigh and arm pressure can be established at this time. However, with data from a larger series of cases, it might be possible to predict the normal blood pressure in the thigh from a knowledge of the arm blood pressure and circumference of the arm and thigh.

To reduce to a minimum the number of variables in this study, the blood pressures in the arm and thigh were measured with a standard-width cuff, even though it is recommended[1] that, in the lower extremity, a cuff containing a rubber bag 2 cm. wider than the standard be employed. This exception was taken for other reasons: (1) The construction of the cuff used in this study prevented slipping and bulging on heavy, tapered limbs, even when it was inflated, and therefore seemed to eliminate the need for a cuff 2 cm. wider; (2) the work of Ragan and Bordley[14] indicates that, in subjects with heavy limbs, if an extra-wide cuff fitted with a locking device to prevent bulging or slipping is employed, the blood pressure readings are frequently too low as compared with direct intra-arterial measurements; and (3) it is desirable to establish normal standards, based on the use of a stand-

ard-width cuff, so that routine estimation of the blood pressure in the thigh is rendered more practicable; a special-sized cuff would defeat this purpose.

SUMMARY

1. Employing the standard auscultatory method for measuring blood pressure, average values for the lower extremities of 500 normal male subjects were obtained.

2. The average arterial pressure in the thigh, with the subject in the horizontal position, is 154.8 mm. Hg, systolic, and 91.9 mm., diastolic, and, in the arm, 118.3 mm., and 70.6 mm., respectively.

3. The influence of soft tissue mass on the blood pressure estimation is discussed. Evidence is presented to support the thesis that the higher arm and thigh pressures recorded in heavy subjects by the indirect method are probably influenced in part by the thickness of the limb.

4. No equipment other than that ordinarily employed for estimating the pressure in the arm was used for the thigh.

The authors wish to thank Robert E. Shilling, First Lieutenant, A.C., who assisted with the statistical analysis.

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A COMPARISON OF THE ACTIONS OF FOUR CARDIAC GLYCOSIDES ON A PATIENT WITH CONGESTIVE HEART FAILURE

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IN THE course of studies dealing with the circulatory effects of the cardiac glycosides, we encountered a patient on whom a series of observations were made which to us seemed of particular interest.

The several cardiac glycosides are known to show differences in their action.[1-5] A full knowledge of these differences requires that many components of the circulation be examined (simultaneously, if possible) during the action of the glycosides on patients with congestive heart failure. Ideally, the circulation should be studied in the same patient when therapeutic doses of the different glycosides are given successively in equal gram-molecular amounts during like degrees of circulatory failure. Such a situation is rarely attained. As a rule, the circulation compensates partially or completely after the administration of the first glycoside, and this renders a comparable state for further observations impossible. In the present case, congestive circulatory failure returned to relatively the same status after the temporary improvement produced by each of a series of glycosides. It was then possible to compare the glycosides under conditions simulating the ideal. This comparison is here reported.

In studying the effects of drugs on congestive heart failure, the cardiac glycosides present certain advantages over digitalis leaf. Preparations of digitalis have the disadvantage of unknown and variable composition.[6] The glycosides are available in pure crystalline form and their chemical structure is known. The complete glycoside consists of a sterol nucleus to which is attached at carbon 17 a butyrolactone ring, at carbon 3 a desoxy-sugar, and, to the desoxy-sugar, several monosaccharide units may be attached.[7]

In this study, four glycosides were employed: lanatoside C, digoxin, digitoxin, and ouabain. Of these, only lanatoside C has all of the component structures outlined above. On hydrolysis, lanatoside C yields digoxin plus a monosaccharide (in this instance glucose) and acetic acid.[6, 7] By similar hydrolysis, digitoxin is derived from lanatoside A or purified glycoside A, and ouabain (strophanthin) from strophanthus gratus. By employing these four purified substances, we were pre-

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pared to compare a structurally complete glycoside (lanatoside C) with its first hydrolysis product (digoxin), and that product with similarly derived hydrolysis products (digitoxin, ouabain) of other structurally complete glycosides.

METHODS

All of the observations were made on the same patient, a 48-year-old woman with moderately severe congestive heart failure. The cause of her heart disease remained uncertain, but it was considered to be of the rheumatic type. There were no valvular defects. The rhythm was uncontrolled auricular fibrillation, with a rapid ventricular rate.

The patient was given, successively, several cardiac glycosides,* administered in equal gram-molecular amounts, as follows: lanatoside C, 0.63 mg.; digoxin, 0.5 mg.; digitoxin, 0.5 mg.; and ouabain, 0.375 mg. This amounts to the administration of equal numbers of molecules of each drug, and permits a comparison of the glycosides in terms of molecule for molecule. The digitoxin was administered as digitaline Nativelle, a commercial preparation which is considered to contain at least 90 per cent crystalline digitoxin. The only other medication received by the patient throughout the study consisted of laxatives and mild sedatives.

The glycosides were always given intravenously. This was done for two reasons: (1) to eliminate differences in absorption of the drugs, and (2) to induce therapeutic effects quickly (within several hours). When the heart failure is relieved partially or completely within several hours, observations can be made continuously throughout the entire period of recovery. This permits primary effects to be readily recognized and differentiated from secondary effects. Such a differentiation is not always possible when observations are made at intervals of many hours or days.

The glycosides were given only when the patient had congestive heart failure. Each glycoside induced a prompt therapeutic effect which persisted for several days, after which heart failure reappeared. Another glycoside was then administered. It cannot be maintained that the degree of congestive circulatory failure was *exactly* similar each time a glycoside was given, particularly because the decompensation seemed to become more severe toward the close of the study. However, by giving each drug (except lanatoside C) twice, and the second dose during a somewhat different state of the circulation, it was possible to compare the different glycosides at quite similar degrees of congestive circulatory failure.

Before a glycoside was given, the patient showed certain subjective and objective signs which indicated that the circulation had lapsed into relatively comparable states of failure. These were complaints of dyspnea, nervousness, restlessness, sweating, and precordial discomfort; a ventricular rate of 150 per minute, or more, for at least two days, usually three; and elevation of the venous pressure to 140 mm. to 150 mm. of saline. Usually five days elapsed between the successive injections of the glycosides. Once eight days elapsed before the above criteria were present. The last glycoside was given after an interval of but three days. The patient had suddenly developed cerebral infarction;

*The authors wish to thank the following companies for generous supplies of the drugs used in this study: Burroughs Wellcome and Company, Inc. (digoxin); Carroll Dunham Smith Pharmacal Company (ouabain); Labatoire Nativelle, Paris (digitaline Nativelle); Sandoz Chemical Works, Inc. (lanatoside C).

digitalis was considered immediately necessary, and the above criteria were discarded.

A number of components of the circulation were measured frequently, and often simultaneously, before and during the action of each glycoside. The ventricular rate was counted, always for a full minute, by auscultation over the precordium. The arterial blood pressure was measured

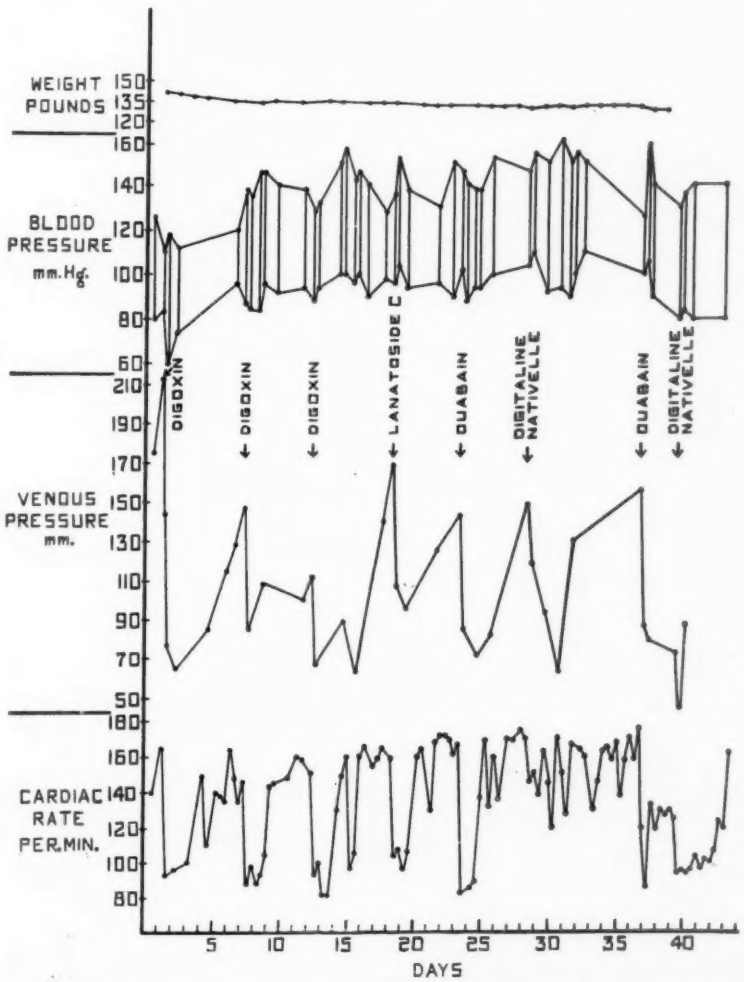

Fig. 1.—General course of several circulatory components throughout the study. Excepting the first dose of digoxin (1.5 mg.), the glycosides were given in equal gram-molecular doses: digoxin, 0.5 mg., lanatoside C, 0.63 mg., ouabain, 0.375 mg., and digitaline Nativelle, 0.5 mg.

by the usual ascultatory method (with mercury manometer). Electrocardiograms were obtained by standard limb leads. Venous pressure was measured in the antecubital veins by the direct method, using a saline manometer. The vein and manometer were always levelled at the same point, namely, 5.5 cm. posterior to the angle of Louis. Respiration was registered by a pneumograph encircling the chest. The volume of blood flow to the hand and calf (two dissimilar vascular areas) was

measured simultaneously by the plethysmographic method. The volume blood flow was measured during resting conditions and during the reactive hyperemia immediately after a five-minute period of ischemia. Teleoroentgenograms and roentgenkymograms were made two to three hours before the injection of a glycoside, and again three to four hours after injection, when therapeutic effects were established. After decided slowing of the ventricular rate had occurred, vagal influence was abolished by the intravenous injection of 2.0 mg. of atropine sulfate, usually given one and one-half to two hours after the administration of the glycoside.

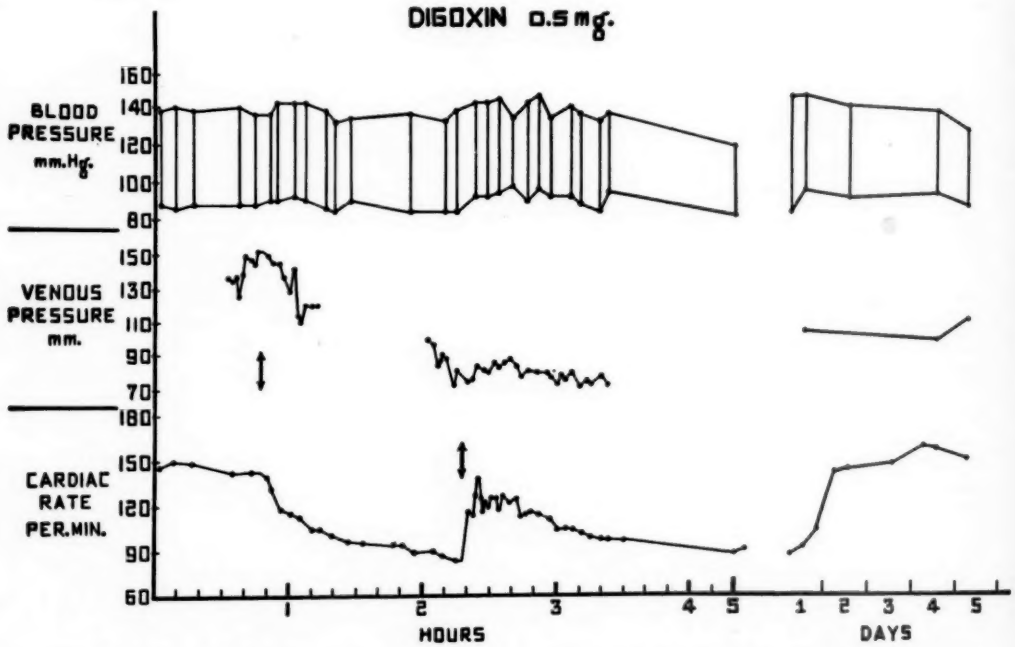

Fig. 2.—Circulatory effects induced by 0.5 mg. digoxin administered intravenously. Degree of decompensation moderate. In this and subsequent charts the following obtains: The data of each chart are from the control period before injection of a glycoside to and including the control period before the next glycoside. The first vertical double arrow indicates injection of the glycoside, the second arrow injection of atropine sulfate.

The observations were made in the morning, with the patient in a fasting state. One study (the second injection of ouabain) was carried out in the evening, when the sudden occurrence of more severe heart failure demanded immediate treatment.

RESULTS

The course of several circulatory components throughout the period of study is presented in Fig. 1, which shows the comparative effects produced by the four glycosides. The ventricular rate generally remained at 150 to 160 per minute. After each glycoside the rate fell sharply to normal, where it remained for several days. It then rose quickly to its previous high level. An abrupt fall of the venous pressure to normal

and a slight increase in the arterial pulse pressure accompanied each decrease in ventricular rate. The venous pressure tended to return to its former high level more slowly than the ventricular rate. The changes in ventricular rate and venous pressure were relatively short-lived, and their duration was comparable when digoxin, lanatoside C, and ouabain were given. When digitaline Nativelle induced similar changes, they were slower in their onset and longer in duration (Tables I and II).

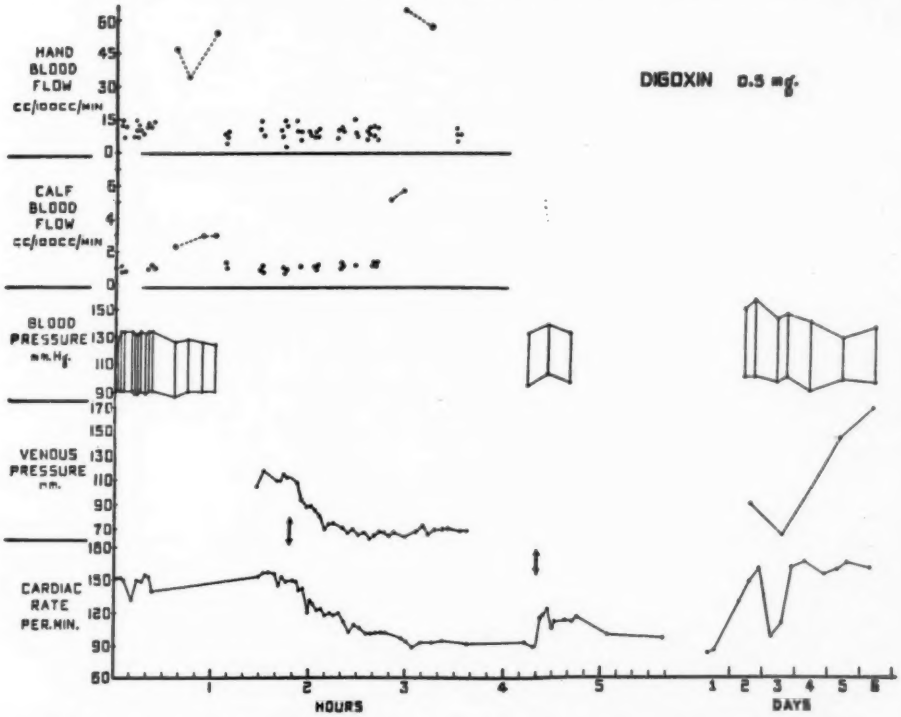

Fig. 3.—Circulatory effects induced by 0.5 mg. digoxin administered intravenously. Degree of decompensation moderate. In this and subsequent charts the volume of blood flow to the hand and calf during the resting state is indicated by the unconnected solid dots; blood flows during reactive hyperemia are connected by the dotted lines. Each dot represents a measurement of blood flow.

Each subsequent chart (Figs. 2 to 8) shows the effects produced by a glycoside from the time of its injection until the next drug was given. The charts are presented in the order in which the drugs were administered. The effect of the first dose of digoxin is not graphed because the amount (1.5 mg.) given exceeded the calculated, equal, gram-molecular dose. Rather than analyze the charts in detail, the circulatory effects of the glycosides will be indicated in relative terms.

Ventricular Rate (Table I).—Ouabain decreased the ventricular rate most rapidly; initial slowing was noted within three to four minutes (Figs. 5 and 7). Several hours elapsed before significant slowing occurred after digitaline Nativelle (Figs. 6 and 8), and the full effect was

TABLE I

EFFECT OF THE CARDIAC GLYCOSIDES ON THE VENTRICULAR RATE

DATE	GLYCOSIDE	DOSE IN MG.	CONTROL* VENTRICULAR RATE PER MINUTE	ONSET OF VENTRICULAR SLOWING MINUTES	PERCENTAGE DECREASE IN VENTRICULAR RATE BELOW CONTROL VALUE: TIME AFTER INJECTION OF GLYCOSIDE															
					10 MIN.	20 MIN.	30 MIN.	1 HOUR	2 HOURS	1 DAY		2 DAYS		3 DAYS		4 DAYS		5 DAYS	
										A.M.	P.M.	A.M.	P.M.	A.M.	P.M.	A.M.	P.M.	A.M.	P.M.
12/23/41	Digoxin	1.5	160-185 (165)	4-8	15.2	28.4	37.6	40.5	43.6	41.2		39.4		21.2	35.8	15.1	18.8	0.6	18.8
12/29/41	Digoxin	0.5	142-150 (146)	3	19.2	28.0	30.8	35.6		34.2	28.0	2.1	0.7	0		0	0		
1/ 3/42	Digoxin	0.5	140-157 (151)	8-11	20.6	21.8	20.6	32.4	39.8	45.7	45.7	15.9	0	35.0	0	0	0	0	0
1/ 9/42	Lanatoside C	0.63	154-174 (159)	7-9	8.8	14.5	18.2	28.4	35.2	40.4	33.4	0	0	18.2	0	0	0		
1/14/42	Ouabain	0.375	155-174 (167)	2-4	22.2	34.2	41.3	44.3	50.4	46.8	16.8	22.2	4.2	18.6	0	0	0		
1/19/42	Digitoxin	0.5	162-176 (170)	45-48	2.9	7.1	5.9	5.9	6.5	29.4	10.6	35.3	11.2	25.3	1.7	3.5	5.9	0	0
1/27/42	Ouabain	0.375	174-180 (176)	1-3	26.8	22.9	29.0	23.8	29.6	49.5	31.2	27.3	26.2						
1/30/42	Digitoxin	0.5	122-132 (125)	30-34	0	0	0	13.6	30.4	24.8	17.7	22.4	18.4	14.4	0.8	0			

*The number in parenthesis indicates the most representative rate.

TABLE II

EFFECT OF THE CARDIAC GLYCOSIDES ON THE VENOUS PRESSURE

DATE	GLYCOSIDE	DOSE IN MG.	CONTROL VENOUS PRESSURE	ONSET OF FALL	PERCENTAGE DECREASE IN VENOUS PRESSURE BELOW CONTROL LEVEL: TIME AFTER INJECTION OF GLYCOSIDE									
			MM. SALINE	MINUTES	10 MIN.	20 MIN.	30 MIN.	1 HOUR	2 HOURS	1 DAY	2 DAYS	3 DAYS	4 DAYS	5 DAYS
12/23/41	Digoxin	1.5	213	8-14	2.3	24.9	21.2		64.0	69.5		60.1	46.0	39.4
12/29/41	Digoxin	0.5	147	15-17	6.1	17.7	20.4	32.0	45.0	26.6			32.0	
1/ 3/42	Digoxin	0.5	112	4-6	21.4	37.4	36.6	43.0	39.4		20.5	43.7		+25.0
1/ 9/42	Lanatoside C	0.63	169	2-4	16.0	26.0	30.8		37.3			26.0		
1/14/42	Ouabain	0.375	143	3	28.7	30.0	39.8	38.4	39.8	49.6	42.7			
1/19/42	Digitaline Nativelle	0.5	149	32-34	0	4.7	0	15.4	22.2	36.9	57.5	12.7		
1/27/42	Ouabain	0.375	156	2	29.5	39.8	43.5	44.8		49.4				
1/30/42	Digitaline Nativelle	0.5	73	25-28	4.1	+20.6	10.9	38.4						

not apparent until the next day. Between these two were digoxin and lanatoside C; digoxin was slightly more rapid in its action. The ventricular rate began to slow within three to eight minutes after digoxin (Figs. 2 and 3), and within seven to nine minutes after lanatoside C (Fig. 4). The final quantitative effect produced by a given glycoside varied somewhat with the degree of decompensation, but the pattern of the response to each glycoside remained the same (compare digoxin Fig. 2 with Fig. 3, ouabain Fig. 5 with Fig. 7, and digitaline Nativelle Fig. 6 with Fig. 8; Table I).

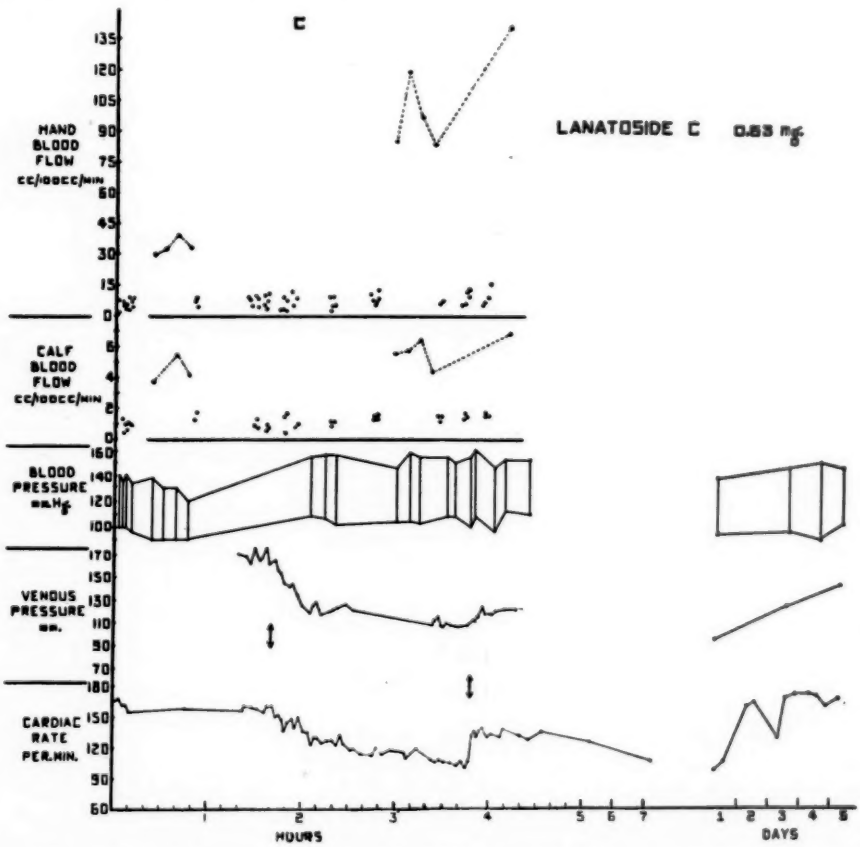

Fig. 4.—Circulatory effects following 0.63 mg. lanatoside C administered intravenously. Degree of decompensation quite severe. In this and subsequent charts the letter *C* indicates the point at which the Cheyne-Stokes respiration disappeared following administration of the glycoside.

Venous Pressure.—The venous pressure fell rapidly to normal after the administration of each glycoside (Table II). Again, ouabain initiated effects most rapidly, within three minutes (Figs. 5 and 7), and digitaline Nativelle most slowly, after twenty-five to thirty minutes (Figs. 6 and 8). After both digoxin (Figs. 2 and 3) and lanatoside C

(Fig. 4), the initiation of effect, four to eight minutes, was but slightly less rapid than after ouabain.

The decrease in venous pressure did not necessarily parallel the slowing in ventricular rate. For example, the first administration of digitaline Nativelle (Fig. 6) induced a considerable fall in the venous pressure but very little change in the ventricular rate. After lanatoside C (Fig. 4), the venous pressure decreased more rapidly than the cardiac rate. Ouabain on each of two trials lowered the venous pressure to 88 mm. of saline (Figs. 5 and 7). The concomitant changes in cardiac rate differed considerably. On the first occasion the ventricular rate fell to 90 per minute (Fig. 5), and, on the second, to 120 per minute (Fig. 7).

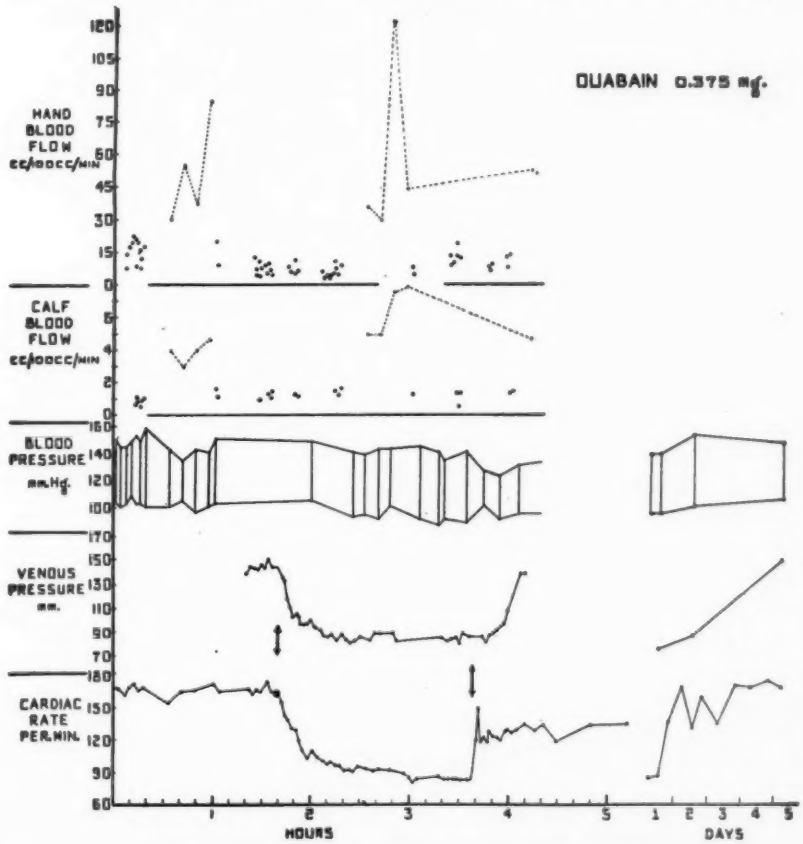

Fig. 5.—Circulatory effects induced by 0.375 mg. ouabain administered intravenously. Degree of decompensation moderate. Atropine sulfate caused much tenseness, restlessness, and involuntary muscular movements. To this was attributed the rise in venous pressure after atropine.

Finally, when vagal tone was released by the injection of atropine sulfate at a time when therapeutic effects had become established, the ventricular rate increased sharply, but the venous pressure remained unchanged (Figs. 2 and 4).

Arterial Blood Pressure.—After the injection of the glycosides the systolic pressure usually rose, whereas the diastolic pressure remained relatively constant. As a result, the pulse pressure increased. These changes were most marked when the circulation was very poor and the pulse pressure small, for example, after the second injections of ouabain (Fig. 7) and digitaline Nativelle (Fig. 8). When the circulation was somewhat better and the pulse pressure was already normal, the arterial pressure remained relatively constant, even though the venous pressure and ventricular rate decreased markedly; for example, the first injection of digoxin (Fig. 2).

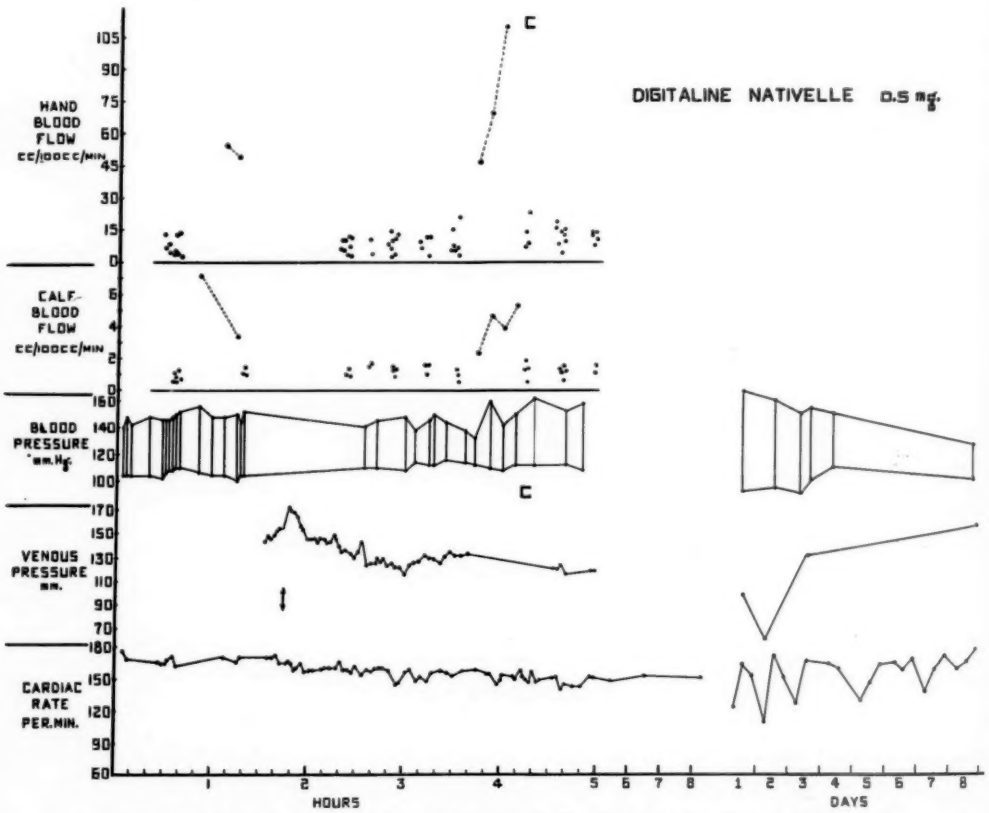

Fig. 6.—Circulatory effects induced by 0.5 mg. digitaline Nativelle given intravenously. Degree of decompensation quite severe.

Peripheral Blood Flow.—The return of the venous pressure and ventricular rate to normal was not accompanied by a significant alteration in the volume of blood flow to the resting hand and calf (Figs. 3, 4, 5, and 6). During reactive hyperemia the blood flow changed equivocally, or not at all, and often the changes in the blood flow to the hand were not even in the same direction as those to the calf (Figs. 3, 4, 5, and 6).

Respiration.—On three occasions Cheyne-Stokes respiration was present when a glycoside was given (lanatoside C, ouabain, digitaline Nativelle). Normal respiration was restored fourteen minutes after lanatoside C (Fig. 4), and twenty-eight minutes after ouabain (Fig. 7), but more slowly, fifty-two minutes, after digitaline Nativelle (Fig. 6).

Electrocardiograms.—The initial therapeutic effects induced by the four glycosides were not accompanied by significant changes in the electrocardiogram, other than a slowing of the ventricular rate.

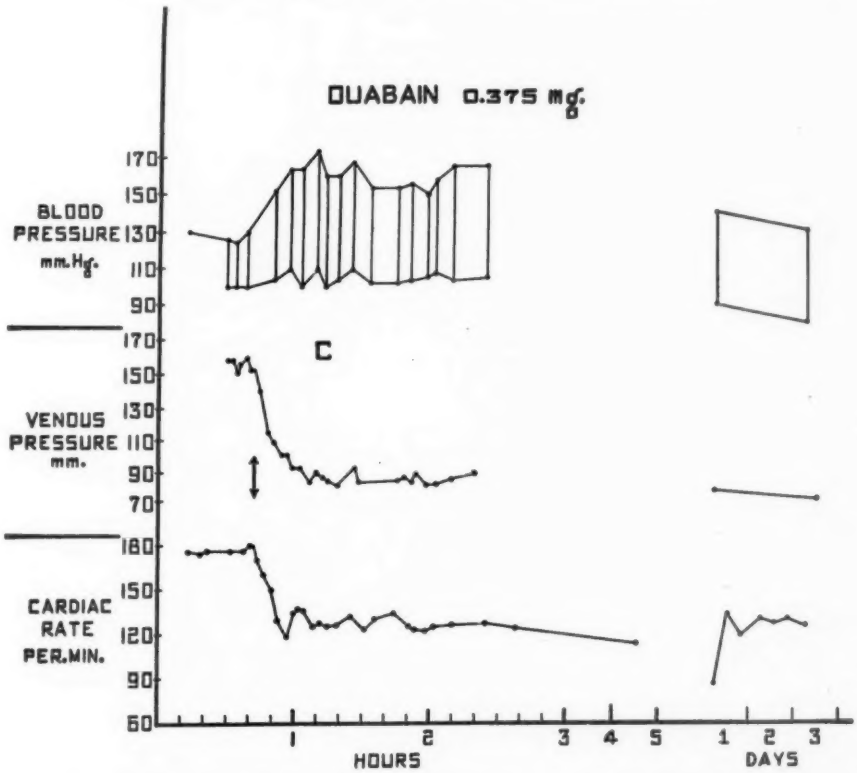

Fig. 7.—Circulatory effects induced by 0.375 mg. of ouabain given intravenously. Patient had incipient pulmonary edema and the degree of decompensation the most severe throughout the study.

Teleoroentgenograms.—The size and shape of the cardiac silhouette showed no, or little, change when teleoroentgenograms made during the initial therapeutic effects were compared with those taken before administration of the glycosides.

Release of Vagal Tone.—After the injection of 2.0 mg. of atropine sulfate, the ventricular rate increased sharply. It usually reached a maximum which was midway between the high initial value before the injection of the glycosides and the lowest value before the atropine was

administered (Figs. 2, 3, 4, and 5). This increase in ventricular rate was not accompanied by a significant change in venous pressure, arterial blood pressure, or volume of blood flow to the calf and hand.

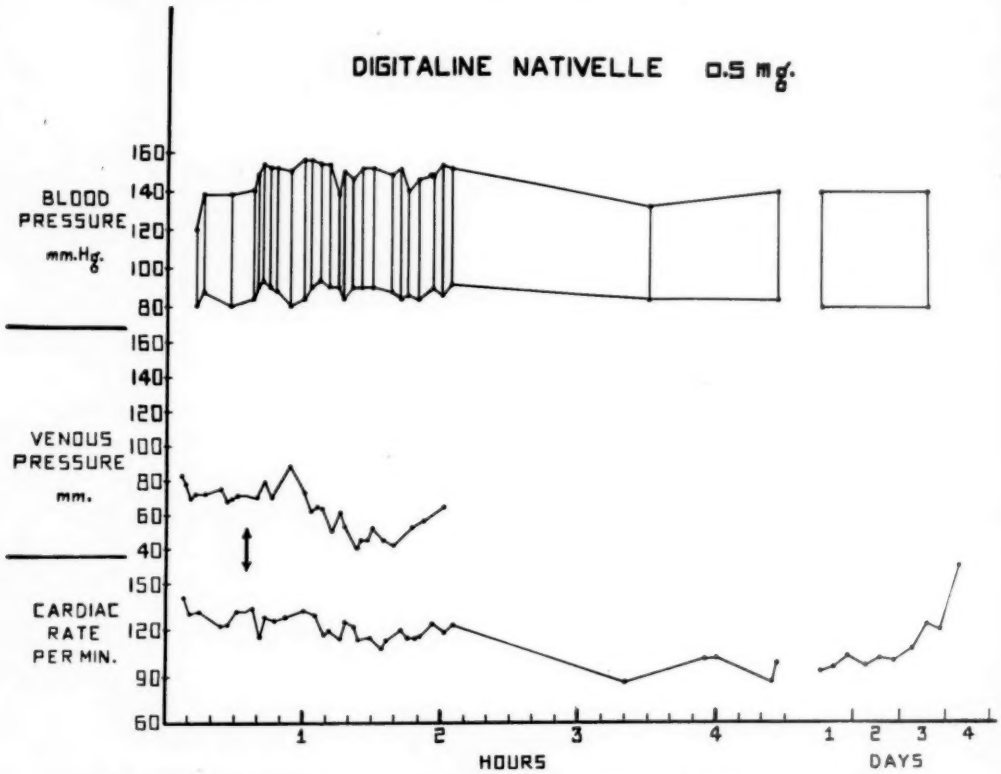

Fig. 8.—Circulatory effects induced by 0.5 mg. digitaline Nativelle given intravenously. Decompensation was less than at any other time, but patient was stuporous because of cerebral infarction.

DISCUSSION

This study is reported because the four glycosides were compared under conditions which were more adequately controlled than is usually possible. From observations on one patient a final concept cannot be formulated concerning the mode of action of these glycosides or the differences between them. However, it is significant that studies on other patients who recovered from heart failure after taking a single glycoside confirm many of the data here presented.

The administration of equal gram-molecular doses permits a comparison of the glycosides in terms of molecule for molecule. This is not necessarily equivalent to a comparison in terms of effective or therapeutic doses. It was not the purpose of this study to ascertain whether varying the dose of a glycoside would change the rapidity with which it produced effects. Certainly, compared molecule for molecule, ouabain achieved therapeutic effects most rapidly, and digitaline Nativelle most slowly.

Between these two, but resembling ouabain more closely, were digoxin and lanatoside C; the former was slightly more rapid in its action. These differences in the actions of the glycosides are not yet explicable on the basis of their chemical structure or physical chemical properties.

When administered intravenously, the cardiac glycosides induced changes in several of the components of the circulation with surprising rapidity. Most noteworthy was the rapid reduction of the elevated venous pressure to normal (usually within thirty minutes to two hours). This change did not necessarily parallel the change in ventricular rate. It occurred without significant alteration in the volume of the peripheral blood flow and without change in the size and shape of the cardiac silhouette. Concomitantly, Cheyne-Stokes respiration disappeared.

In the absence of data on cardiac output, this study does not explain the mode of action of the cardiac glycosides. It does, however, indicate a method which, when amplified by the addition of serial measurements of cardiac output, gives promise of clarifying the controversy[8-11] concerning the mode of action of digitalis and its component glycosides.

SUMMARY

1. In a case of auricular fibrillation and congestive heart failure the circulation compensated promptly, but temporarily, after each intravenous administration of lanatoside C, digoxin, digitaline Nativelle, and ouabain. The drugs were given successively and in equal gram-molecular amounts.

2. When compared molecule for molecule, ouabain initiated effects most rapidly, and digitaline Nativelle most slowly. Between the two, but resembling ouabain more closely, were digoxin and lanatoside C; the former was slightly more rapid in its action.

3. When the cardiac glycosides were administered intravenously they produced abrupt changes in several circulatory functions without alterations in others:

a. Elevated venous pressure fell quickly to normal.

b. Rapid ventricular rate slowed promptly.

c. Diminished arterial pulse pressure increased as a result of elevation of the systolic pressure.

d. Volume of the blood flow to the calf and hand remained unaltered.

e. Cheyne-Stokes respiration speedily disappeared.

f. Cardiac size and shape did not change.

g. Electrocardiograms showed only a slowing of the ventricular rate.

The authors wish to thank Dr. Arthur C. DeGraff for his advice and helpful criticism throughout this study. This investigation was conducted with the technical assistance of Miss Bertha Rader and Miss Helen Pomykala.

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SUBARACHNOID HEMORRHAGE CAUSED BY RUPTURED INTRACRANIAL ANEURYSM

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THE term "spontaneous subarachnoid hemorrhage," which has been used for many years to designate meningeal bleeding of nontraumatic origin, is confusing and meaningless, and should be discarded. This viewpoint was emphasized by Smith,[1] Ayer,[2] and Sands.[3] In the majority of instances, such conditions as ruptured intracranial aneurysm, extension of a massive cerebral hemorrhage into the subarachnoid space, hemorrhage from a neoplasm, meningeal inflammation, or a blood dyscrasia can be established as the cause.

Our attention has been directed to the importance of recognizing aneurysm of the circle of Willis and its adjacent branches as the cause of the bleeeding. We feel that aneurysms are responsible for the majority of examples of subarachnoid hemorrhage of nontraumatic origin.

In this report we wish to review the clinical features in 64 cases in which a diagnosis of subarachnoid hemorrhage caused by ruptured intracranial aneurysm was made. We also wish to discuss the pathologic observations on twelve patients who died as the result of rupture of aneurysms located in and around the circle of Willis. In none of these cases was there evidence of bacterial endocarditis or other types of septicemia. We are aware of the possibility that unrecognized trauma, hemorrhage from a neoplasm, or subarachnoid bleeding secondary to massive cerebral hemorrhage might have occurred in the cases in which the patients survived. The clinical features, however, are sufficiently definite to enable one to make the correct diagnosis in the majority of instances. This group of patients was examined at the University Hospital in the ten-year period from 1932 to 1942.

The literature is replete with discussions of aneurysms of cerebral vessels. McDonald and Korb,[4] for example, reported 1,125 cases of saccular aneurysms of arteries at the base of the brain in which the diagnosis was verified by autopsy or operation. Another comprehensive review of the subject was made by Richardson and Hyland,[5] who studied 118 patients with subarachnoid hemorrhage and eight patients with large, unruptured aneurysms over an eleven-year period.

The etiologic factors can be grouped under the following headings: congenital weakness of vessel walls, arteriosclerosis, inflammation, and trauma. The importance of congenital weakness of the vessel walls in

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the production of aneurysms was pointed out by Eppinger,[6] and has been emphasized by Fearnsides,[7] Turnbull,[8] Forbus,[9] and Courville and Olsen.[10] The fact that such hemorrhages have occurred in young persons has led numerous observers to conclude that a congenital defect must be the underlying cause. Anomalies in the vessels of the circle of Willis are thought by some authors to be contributory.[11, 12] On the

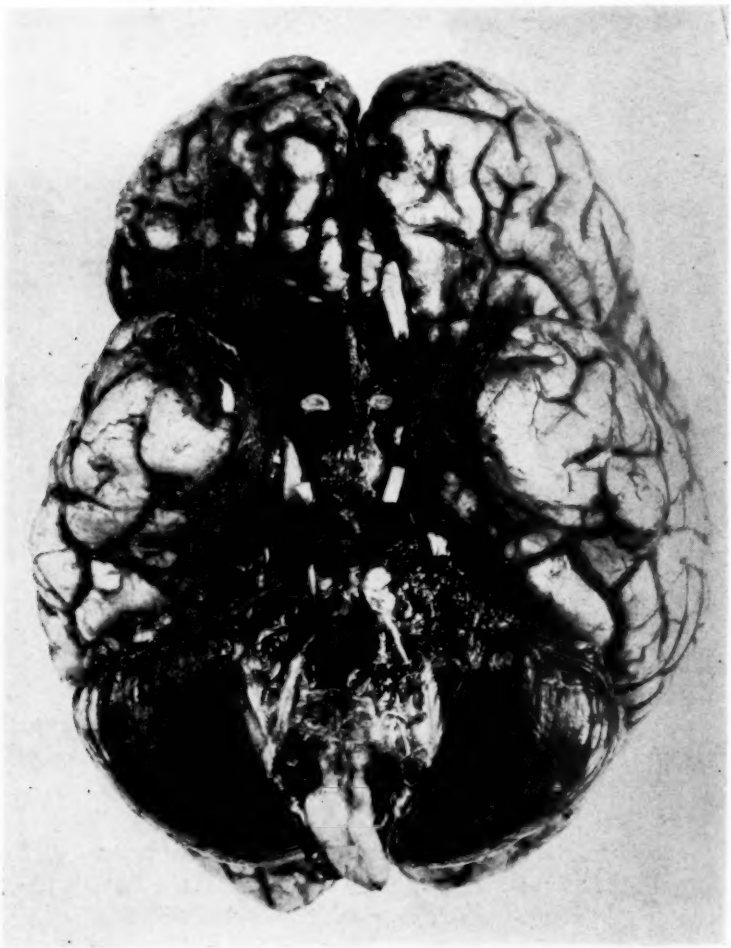

Fig. 1.—Massive subarachnoid hemorrhage resulting from rupture of aneurysm of left internal carotid artery.

other hand, Ellis[13] regarded arteriosclerosis as the cause of these aneurysms. His view was shared by Tuthill,[14] Symonds,[15] and Strauss, Globus, and Ginsburg.[16] "Mycotic" aneurysms have been reported by Ponfick,[17] and Esser.[18] In the opinion of Cushing,[19] many aneurysms of early life are of mycotic, rather than congenital, origin. Syphilis and trauma play a minor role.

The most common finding at autopsy is a mass of clotted blood filling the subarachnoid space at the base of the brain (Fig. 1). Variable amounts of blood are extravasated over the convexity. The hemorrhage may occur into the ventricular system, as well. Occasionally, the blood will dissect through a lobe of the brain, and, rarely, may break into the subdural space (Fig. 2). Sometimes the aneurysm can be found without difficulty in the mass of clotted blood. We would like, however, to emphasize the importance of fixing the entire brain in formalin if the source of bleeding cannot be ascertained at once. In many instances the aneurysm will be found only when careful dissection of the circle of Willis and its adjacent branches is carried out after the brain is properly fixed (Fig. 3).

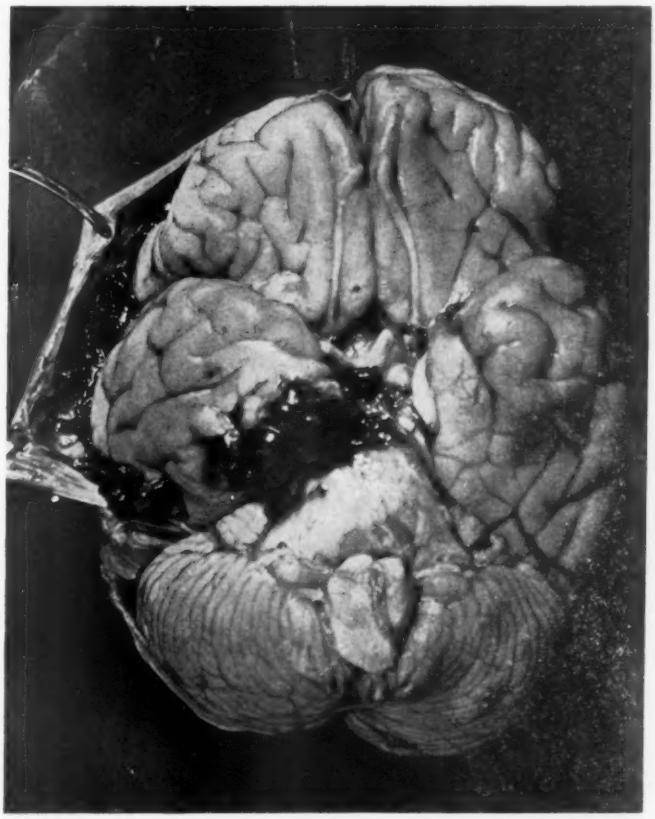

Fig. 2.—Ruptured aneurysm of right internal carotid artery, with extravasation of blood through right temporal lobe and leptomeninges, producing a subdural hematoma over right frontal, parietal, and temporal lobes.

We have examined the aneurysms microscopically in twelve autopsy cases (Table I). Six of the aneurysms were removed in toto, embedded in celloidin, and sectioned serially. The occurrence of these aneurysms at points of bifurcation is a well-established fact (Figs. 3, 4, and 8).

Microscopically, the aneurysmal wall is thin. The vessel, composed principally of fibrous tissue, undergoes progressive stretching and thinning until it ruptures (Fig. 5). In most instances the aneurysmal sac takes various stains poorly; hyalinization is common. The intimal lining is usually intact up to the point of rupture. In some of the specimens,

TABLE I

PRINCIPAL AUTOPSY OBSERVATIONS IN TWELVE CASES OF INTRACRANIAL ANEURYSM

AGE (YR.)	SEX	LOCATION	DIRECTION OF RUPTURE	PROBABLE CAUSE	COMMENTS
33	M	L. int. Carotid	Subarachnoid space	Congenital	Death after craniotomy Leptomeninges extensively thickened
51	F	L. int. Carotid	Subarachnoid space Intraventricular via floor of third ventricle	Congenital	Small right internal carotid and left vertebral arteries
32	M	L. post. Cerebral	Subarachnoid space	Congenital	Positive Wassermann Extensive vascular syphilis in arteries other than aneurysm
51	M	R. ant. Cerebral	Subarachnoid space Intracerebral (frontal)	Inflammatory (?)	Cultures and special stains for bacteria were negative
24	M	L. int. Carotid	Subarachnoid Intracerebral (frontal) Intraventricular	Congenital	Polycystic kidney disease
59	M	R. middle Cerebral	Subarachnoid Intracerebral (temporal) Intraventricular	Congenital	Extensive arteriosclerosis elsewhere; encephalomalacia, right parietal lobe
45	M	R. middle Cerebral	Subarachnoid Intracerebral (temporal)	Arteriosclerotic	Encephalomalacia, right temporal
37	M	Basilar	Subarachnoid Intraventricular via floor of third ventricle	Congenital	
38	F	R. int. Carotid	Subarachnoid Intracerebral (temporal) Subdural	Congenital	Massive, recent, subdural hemorrhage
53	M	Ant. Communicating	Subarachnoid Intracerebral (frontal) Intraventricular	Inflammatory	Acute arteritis at point of rupture
44	M	Ant. Communicating	Subarachnoid Intracerebral (frontal) Intraventricular	Congenital	Anomalous anterior cerebral arteries
45	F	R. middle Cerebral	Subarachnoid Intracerebral (temporal)	Congenital	Polycystic kidney disease

Fig. 3.—Small aneurysm located at the first bifurcation of the right middle cerebral artery. Although the point of rupture was not demonstrated grossly, it was readily identified in serial sections after embedding the specimen in toto in celloidin.

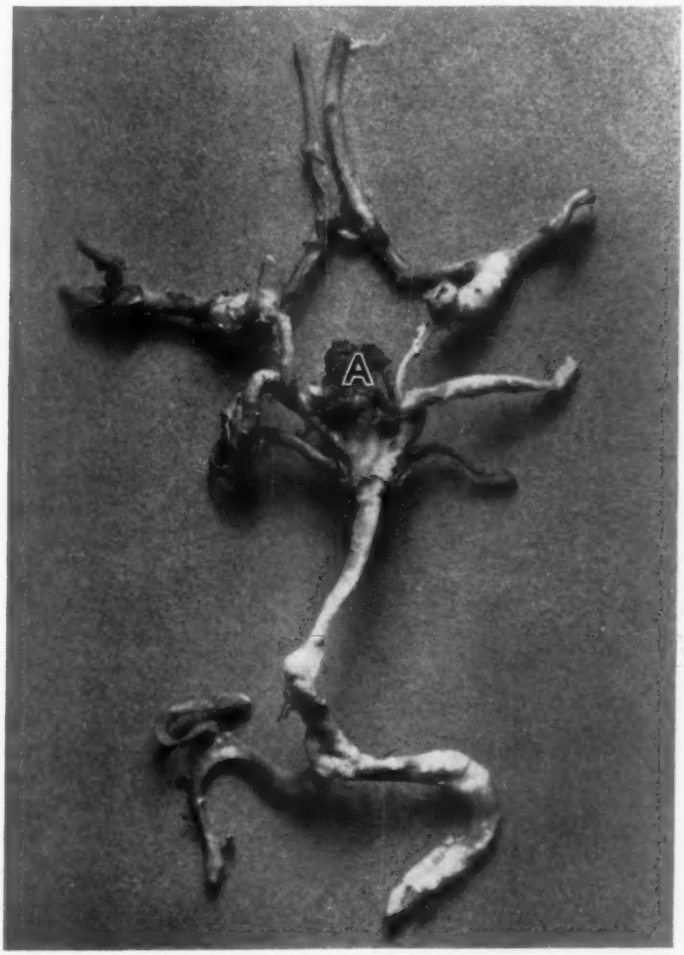

Fig. 4.—Dissection of entire circle of Willis to show ruptured aneurysm of basilar artery (*A*) at the point at which it bifurcates to form the two posterior cerebral arteries.

irregular thickening of the subintimal zone is seen (Fig. 5). In nine of the twelve specimens it was possible to demonstrate, with Weigert's elastic tissue stain, the presence of an internal elastic membrane which was very attenuated and defective, particularly at the points of rupture (Fig. 6). Occasionally one finds bits of media, but the amount of muscle tissue is so small as to be almost valueless from the functional standpoint. In most instances, no inflammatory reaction is present. In two of the specimens, however, some infiltration of the aneurysm wall by inflammatory cells, principally lymphocytes, was seen (Fig. 7). In one of these (Fig. 7), a zone of inflammatory elements extended through the wall at a place removed from the point of rupture. The basic aneurysmal process, especially fragmentation of the media, remains the same. In the other specimen the appearance was more nearly that of a true mycotic aneurysm. By way of summary, then, the following changes are seen in greater or lesser degree: thinning of the aneurysmal wall, hyalinization and fibrosis of the wall, proliferation of the intima, attenuation and straightening of the elastic membrane, thinning or absence of the media, and cellular infiltration.

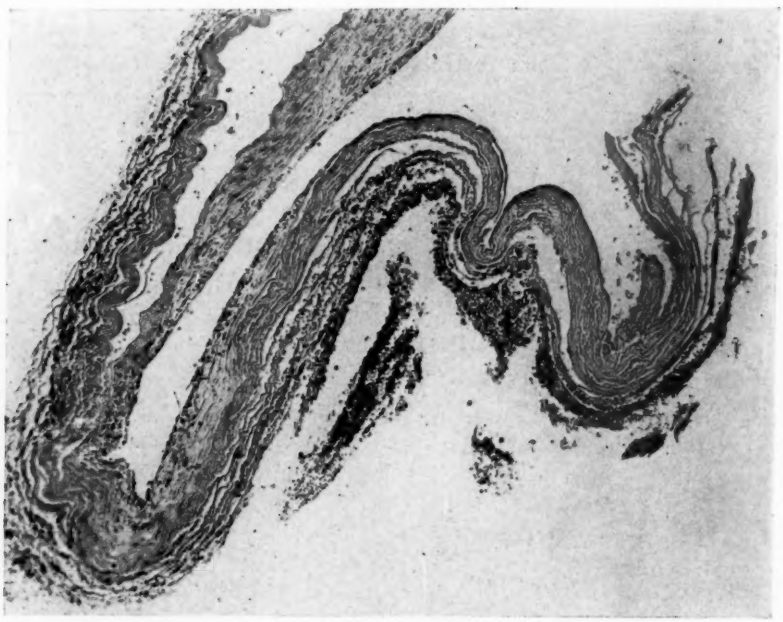

Fig. 5.—Aneurysm located at first bifurcation of right middle cerebral artery. Although there was extensive arteriosclerosis elsewhere, aneurysmal wall is thin. There is extensive fragmentation of vessel wall, especially at the point of rupture. One small area of intimal thickening is seen. Hematoxylin-eosin stain. ×75.

From our observations, we would subscribe to the theory of congenital weakness of the vessel wall as the factor responsible for the majority of these aneurysms. Our studies indicate that, for the most part, we are dealing with a long-standing disorder which results in progressive

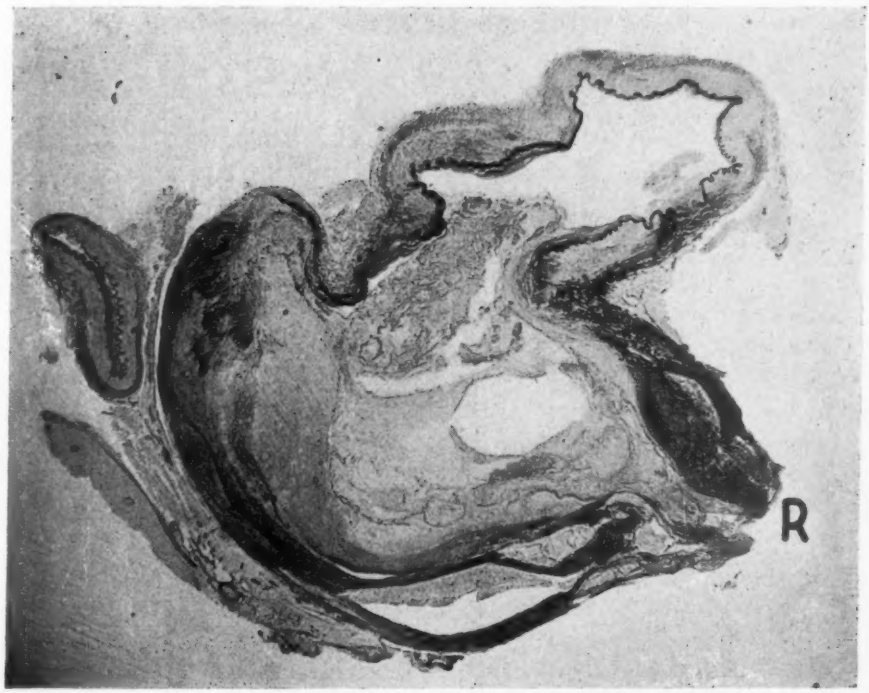

Fig. 6.—Aneurysm of the first bifurcation of the right middle cerebral artery. The point of rupture is at (*R*). Note the fragmentation of the elastic layer and the patchy thickening of the intimal layer. Weigert's elastic tissue stain, ×15.

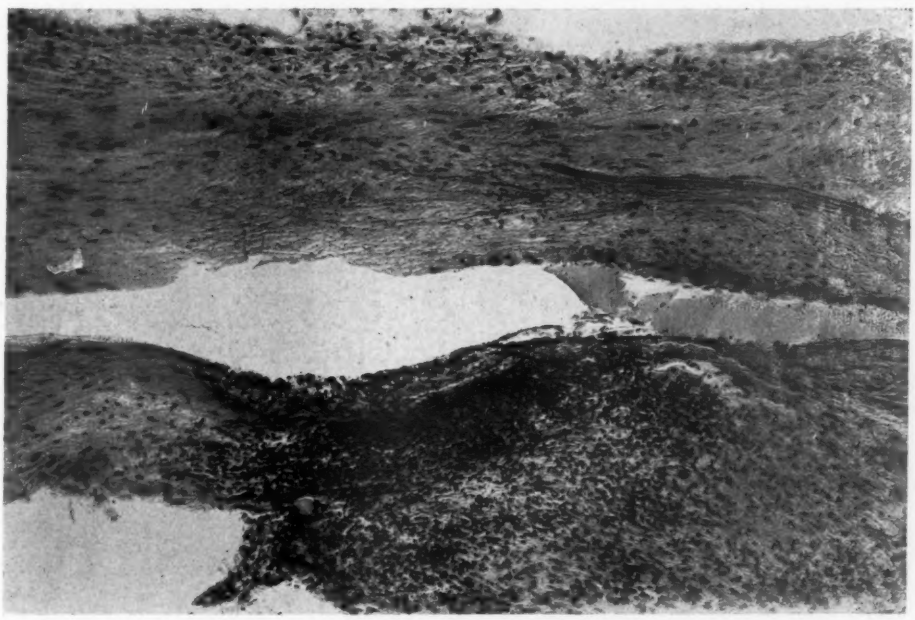

Fig. 7.—Aneurysm of right middle cerebral artery, showing zone of inflammatory cells in only one portion of the wall at some distance from point of rupture. The thinning of the wall, fibrosis, and defect in elastica are well seen. Hematoxylin-eosin stain, ×75.

stretching of the vessel wall to the bursting point. The occurrence of these lesions at bifurcations, the presence of anomalies in the circle of Willis (Figs. 8 and 9) and other conditions, such as polycystic kidney disease, further strengthen the theory of the congenital nature of these aneurysms. Elevated blood pressure probably plays a part in the ultimate rupture of the vessel. It is difficult to evaluate the importance of other factors, such as ageing of the vessel and toxic or degenerative influences.

A common immediate sequel to rupture of a vessel of the circle of Willis or its larger branches is extravasation of blood into the subarachnoid space (Fig. 1, Table II). The irritating effect of blood produces signs and symptoms of meningitis. Another phenomenon which is often encountered is the local pressure effect of the enlarging aneurysm or of the effused blood. The optic nerves and tracts and the oculomotor nerves are often involved. Blood may be forced through the brain substance, with the production of other focal signs. Intraventricular rupture has been frequent in the cases in which the patients died (Table I).

The condition under consideration is a disease of middle age. The average age of our patients was 43 years. The oldest patient in our series was 72 years of age, and the youngest, 14 years. The sex distribution was approximately equal. In only ten of our cases did some form of severe mental or physical strain precede the rupture; the majority of ruptures occurred during ordinary activity.

The onset is usually abrupt. Characteristically, there is sudden, severe pain in the head or in the back of the neck. The headache is usually of a diffuse type, but in some cases the pain takes a definite localizing character in one temple or behind the eye. Nausea and vomiting occur with considerable frequency. Visual disturbances of one type or another are commonly experienced. Convulsions occur occasionally. When convulsions are present they are usually generalized in type. Consciousness may or may not be lost after rupture of an aneurysm.

The clinical signs are usually quite characteristic. When blood is extravasated into the subarachnoid space, it gives rise to the symptoms of meningitis, namely, stiffness of the neck and a positive Kernig's sign. There is usually a mild febrile reaction which lasts while the blood is being absorbed. A rise of temperature to 103 or 104° F. in the absence of pneumonia and in the presence of increasing coma usually indicates intraventricular bleeding. Hemiparesis or hemiplegia is caused by pressure of the extravasated blood upon the cerebral peduncles, laceration of brain substance by effused blood, or softening of the brain in the area supplied by the involved vessel.

CASE REPORTS

CASE 1 (R. W.).—Rupture of intracranial aneurysm, with subarachnoid hemorrhage, following exertion. Similar attack one month later. Bloody spinal fluid. No localizing signs. No recurrence of symptoms in subsequent seven months.

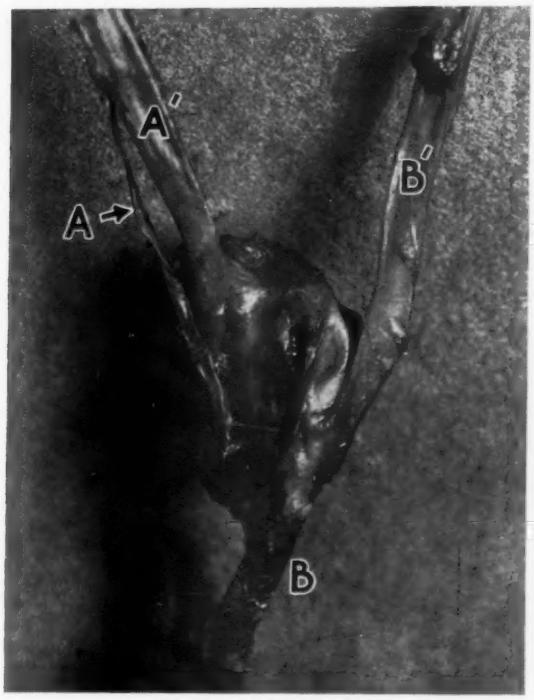

Fig. 8.—Aneurysm of the anterior communicating artery, showing point of rupture. The left anterior cerebral artery (*A*) is rudimentary, and does not communicate with the aneurysm, but joins the large left branch (*A'*) arising from the region of the aneurysm. The major portion of the vascular supply is thus carried through the right anterior cerebral artery (*B*), from which vessel the aneurysm and two normal-sized anterior cerebral arteries (*A'*) (*B'*) emerge.

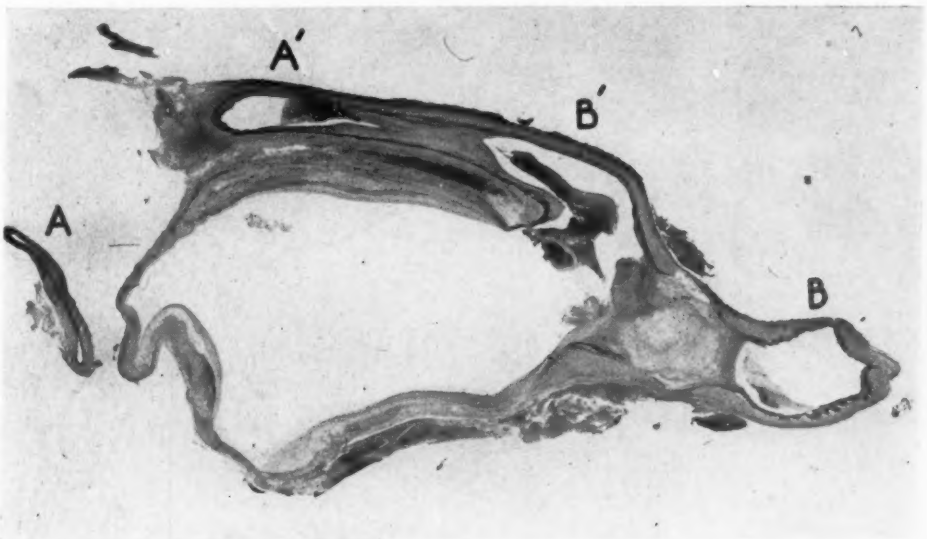

Fig. 9.—Section of aneurysm shown in Fig. 8. Identification markings as above. Weigert's elastic tissue stain, ×6.

TABLE II

SUMMARY OF CLINICAL STUDIES OF 64 PATIENTS WITH SUBARACHNOID HEMORRHAGE

AGE INCIDENCE		SEX INCIDENCE		FACTORS PRECEDING RUPTURE		INITIAL SYMPTOMS		SIGNS*		CLINICAL RESULT AT DISCHARGE	
By decades:		Male	33	Marked exertion	10	Headache	38	Stiff neck	48	Died	18
First	0	Female	31	Mild exertion	32	Vomiting	1	Positive Kernig's sign	28	Well	22
Second	4			None	22	Dizziness	3	Fever	20	With sequelae	24
Third	4					Unconsciousness	8	Hemiparesis or hemiplegia	13	Hemiparesis or hemiplegia	6
Fourth	19					Visual disturbances	3			Ocular palsy	11
Fifth	15					Mental confusion	3	Ocular palsy	12	Visual field disturbances	3
Sixth	16					Convulsions	8	Choked discs	7	Aphasia	2
Seventh	4							Aphasia	4	Other	2
Eighth	2							Visual field defect	4		
Oldest,	72 years							Nystagmus	3		
Youngest,	14 years							Bruit	1		
Average,	43 years							Hypertension (arterial)			
								Marked	8		
								Moderate	20		
								Spinal Fluid Examination			
								Pressure:			
								Over 200 mm.	17		
								Below 200 mm.	47		
								Color:			
								Grossly bloody	32		
								Xanthochromic	16		
								Clear	13		

*Approximately 25 per cent of these patients were admitted to the hospital several weeks after the beginning of the bleeding.

This 14-year-old boy was well until October, 1941, when he developed a severe headache after a short period of exercise. Within fifteen minutes he began to vomit because of the headache. He remained in bed two weeks, during which time his headache gradually subsided. He was well until Nov. 13, 1941, when he suddenly developed headache, again after exertion. He vomited hourly during the night, complained of a stiff neck, and became irrational.

Examination on admission to the hospital on Nov. 14, 1941, showed that he was well developed and well nourished. His temperature was 98.6°, his pulse rate, 72, and his respiratory rate, 20. There was considerable photophobia. His neck was stiff, and Kernig's sign was present. His blood pressure was 110/80. The spinal fluid was under an initial pressure of 175 mm., and was grossly bloody. The blood and spinal fluid Wassermann reactions were negative. Five days later the spinal fluid was under an initial pressure of 105, was xanthochromic, and contained 1,250 erythrocytes per c. mm. Examination of the urine and blood showed nothing remarkable.

For a period of two days after admission he complained of severe headache and vomited frequently. These symptoms gradually subsided, and, by the time of discharge from the hospital, Nov. 22, 1941, he was free of symptoms except for a very mild headache. He had no further attacks up to the time of his last examination, June 6, 1942, at which time he felt well and exhibited no abnormal neurologic signs.

CASE 2 (W. J.).—Three separate subarachnoid hemorrhages. Residual paresis of cranial nerves.

This 56-year-old foundry worker was first admitted to the University Hospital April 4, 1936. His past history was unimportant except for the fact that he had had a fall in 1935, involving the right temporal region, and suffered from a headache for a period of one day. On Feb. 13, 1936, he developed a sudden, severe pain in the right temporal and occipital regions, with vomiting and stupor. Spinal punctures revealed increased pressure and bloody spinal fluid. The second attack occurred Feb. 24, 1936, when, in addition to the severe headache, he developed ptosis of the right upper lid and experienced double vision when the lid was held up.

Examination on admission, April 4, 1936, showed percussion tenderness over the right temporoparietal region, complete oculomotor nerve paralysis on the right side, and evidence of generalized arteriosclerosis. His blood pressure was 130/85, and his blood Wassermann reaction was negative. The spinal fluid examination was negative. He improved slightly with rest in bed and sedatives. At time of discharge his oculomotor paralysis had diminished.

He worked daily until August, 1941, when he was suddenly seized with severe occipital and cervical pain. A spinal puncture revealed bloody fluid. He improved slightly until the time of his second admission to the hospital, Aug. 15, 1941. Additional abnormalities at this time were right abducens paresis and a positive Babinski sign on the left. The spinal fluid was subsequently xanthochromic, was under an initial pressure of 250 mm., and contained 105 mg. of protein per 100 c.c. All of the new signs disappeared, so that, by August 21, he exhibited only the right-sided oculomotor paresis.

He returned to work, but relapsed on Nov. 10, 1941, and again on Dec. 27, 1941. After this last attack he was again admitted to the hospital,

where he remained for several weeks. He refused to have a diagnostic arteriographic examination or exploratory craniotomy performed.

CASE 3 (J. M.).—Two subarachnoid hemorrhages six years previous to the fatal attack. Sudden onset of severe headache after exertion, unconsciousness, slight improvement, then relapse and death in five days. Grossly bloody spinal fluid. Autopsy: congenital aneurysm of anterior communicating artery, with anomalous anterior cerebral artery.

The patient was 44 years old. In December, 1936, this patient suddenly experienced severe headache, vomiting, stiffness of the neck, and bradycardia. There was no loss of consciousness at any time during this attack. Neurologic examination showed no focal cerebral signs. Lumbar puncture eight days later revealed xanthochromic fluid. After the removal of 15 c.c. of spinal fluid he obtained relief from the headache and felt well until January, 1937, when another hemorrhage occurred. In this attack he was unconscious for several weeks. A total of nine spinal drainages were performed. Again, there were no definite signs indicating the exact site of the ruptured vessel. He recovered from this illness much more slowly than from the previous one, but was able to resume his duties as a university professor in the fall of 1937. Neurologic examination at intervals showed nothing abnormal. His blood pressure ranged from 134/84 to 148/96.

On Feb. 26, 1942, he suddenly developed a severe headache following a short period of exertion, and soon became unconscious. One hour later he was admitted to the University Hospital in a stuporous condition. His temperature was 99.8° F. There were several flame-shaped hemorrhages in the right retina. His blood pressure was 220/146. He moved his arms and legs well, but there was a bilateral plantar extensor response. He was incontinent. The spinal fluid, which was grossly bloody, was under an initial pressure of 400 mm. The blood and spinal fluid Wassermann reactions were negative. He improved slightly during the following day, then gradually grew worse. Several more spinal punctures showed a grossly bloody fluid which was under increased pressure. He died on the fifth day. Terminally, his temperature rose to 107° F.

Autopsy was limited to the brain, which weighed 1,700 grams. Extensive hemorrhage was present throughout the entire subarachnoid space, especially around the base. After the brain was fixed in formalin, the vessels of the circle of Willis were dissected out. The right vertebral artery was one-half the size of the left. The anterior cerebral supply was anomalous (Fig. 8). The proximal portion of the left anterior cerebral artery was rudimentary. Most of the blood supply in this region was carried by way of the right branch. In the region of the anterior communicating artery there was a thin-walled aneurysm which measured 2 by 1.5 by 1.5 cm. The point of rupture was readily demonstrated. Two equal-sized anterior cerebral arteries arose from this aneurysm, and the filamentous anterior cerebral artery joined the left branch approximately 3 cm. distal to the aneurysm. There was considerable hemorrhagic softening of the medial surfaces of both frontal lobes. Bleeding had occurred into the ventricles by way of the anterior horns. The aneurysm was embedded in celloidin in toto and sectioned serially.

Microscopic sections were stained with hematoxylin and eosin, Masson's trichrome stain, and Weigert's elastic tissue stain. The aneurysm

(Fig. 9) was thin-walled and fibrotic. Bits of muscle tissue could be identified in the wall, in addition to a few fragmented remnants of the elastic layer. A few patches of intimal thickening were in evidence. There was no sign of inflammation in the wall of the aneurysm.

CASE 4 (D. B.).—Hypertension, headaches, and increasing irritability for five months. Unconsciousness, followed by restlessness and severe headache. Bloody spinal fluid. Second attack three weeks later, associated with convulsions. Death in twenty-five minutes. Autopsy: aneurysm of basilar artery, with rupture through floor of third ventricle and intraventricular hemorrhage.

The patient was 37 years old. This man was refused insurance seven years before admission because of hypertension. Five months before admission he began to complain of headaches which were worse in the morning, and his wife noticed that he was becoming increasingly irritable. However, he continued to work until nine days before admission, when, about 4 A.M. on Sept. 27, 1941, he began to breathe noisily and could not be roused. He recovered consciousness in two hours, then began to vomit. His physician found that his systolic blood pressure was 220 mm. Hg. He was given several hypodermic injections during the day. That evening he became very restless, and was taken to a local hospital, where he became disoriented, and, finally, stuporous.

When admitted to the University Hospital, Oct. 3, 1941, he was very drowsy. His head was retracted and his neck was stiff. Examination of the ocular fundi showed advanced hypertensive retinal disease. His blood pressure was 210/130. Examination of the urine showed a trace of albumin. The blood cell count was normal. The blood Wassermann reaction was negative. The spinal fluid was under an initial pressure of 50 mm., showed a positive Pandy test for globulin, 7 cells, a negative Wassermann reaction, and a positive test for blood.

He improved gradually at first. His drowsiness disappeared and he complained less of headache. During the night of Oct. 15, 1941, he developed a convulsion in his sleep, his respirations became stertorous, and he died within twenty-five minutes.

The brain weighed 1,740 grams. The basilar leptomeninges were filled with clotted blood. After the brain was fixed in formalin the circle of Willis was dissected free. Atheromatous changes were found in all the branches of the circle of Willis. At the bifurcation of the basilar artery there was an aneurysm the size of a cherry (Fig. 4). It had ruptured through the floor of the third ventricle and had filled the entire ventricular system with blood.

Serial sections were made of the basilar aneurysm after it had been embedded in celloidin. A control specimen was prepared from the right middle cerebral artery. These sections were stained with hematoxylin and eosin, Masson's trichrome stain, and Weigert's elastic tissue stain.

Sections of the basilar artery at its bifurcation showed a comparatively large rupture. Although the vessels elsewhere showed advanced atherosclerotic changes, the aneurysm was thin-walled, and consisted mostly of fibrous tissue which contained remnants of media and elastica. Only a few patches of intimal thickening could be seen. There was no evidence of inflammation in the aneurysm wall.

CASE 5 (E. R.).—Sudden onset of severe headache, followed by vomiting. Two days later, a second attack, followed by convulsion and stupor. Blindness, weakness of the right arm and leg. Papilledema, right-sided oculomotor paralysis. Bloody spinal fluid. Third attack ten days later, resulting in death. Autopsy: aneurysm of left internal carotid, with massive rupture through left temporal lobe into the left subdural space.

This 38-year-old housewife was admitted to the University Hospital Jan. 2, 1942, in a stuporous condition. Her husband gave the information that she had been in good health, except for mild epigastric distress, until the afternoon of January 2, when she suddenly called to him that something had broken in her head. She did not fall or lose consciousness, but immediately developed a headache and was forced to go to bed. Approximately five hours afterward she vomited. She remained in bed the following day because of moderately severe headache. On January 4, however, she awakened at 4 A.M., screaming because of pain in her head. She had a brief generalized convulsion and lapsed into stupor. Later in the morning, however, she could be roused. She complained that she was completely blind, and was mentally confused. Her right arm and leg were weak.

On admission to the hospital she was stuporous but responsive. Examination January 5 revealed ptosis of the right eyelid, a dilated and practically immobile right pupil, and external deviation of the right eye. There was bilateral papilledema, with vaginal sheath hemorrhages in both retinae. Vision O.D., 6/30; O.S., light and shadow. Temperature, 102° F., pulse rate, 80, respiratory rate, 18. Her neck was very stiff to anteflexion. The blood pressure was 150/100. Examination of her extremities showed no evidence of weakness or changes in the reflexes or sensations. No bruit could be heard on auscultation of the skull.

Her urine was normal except for a trace of albumin. The erythrocyte count was 5.65 million, the hemoglobin, 14.0 grams, and the leucocyte count, 17,200. The blood smear was normal. The blood Wassermann reaction was negative. The initial pressure of the spinal fluid was 210 mm. with the patient in the horizontal position; the fluid was bloody, contained 40 leucocytes per c.mm., and gave a strongly positive reaction for blood and a negative Wassermann reaction.

She improved gradually, had less headache, and her vision returned. On the morning of January 12 her headache suddenly returned, she cried out, and had a generalized convulsion. Her respirations became shallow and rapid, and she died in forty minutes.

The important autopsy observations were confined to the brain, which weighed 1,450 grams. There were approximately 2½ ounces of freshly clotted blood in the right subdural space over the frontal, temporal, and parietal regions. The blood had come from the right internal carotid artery and had forced its way through the substance of the inferior portion of the right temporal lobe into the subdural space (Fig. 2). Blood had also extravasated into the temporal horn of the right lateral ventricle.

The aneurysm was thin-walled and fibrotic. The adventitia contained a few inflammatory cells, mostly lymphocytes. In other respects, however, the microscopic appearance was the same as that in the previous cases.

DIAGNOSIS

Ordinarily, the diagnosis of this condition is not difficult. The sudden onset of headache, symptoms and signs of meningeal irritation, and the presence of blood in the spinal fluid usually constitute sufficient evidence on which to make a diagnosis. Subarachnoid hemorrhage after trauma or during the course of one of the hemorrhagic disorders should present no unusual diagnostic difficulties. The sudden appearance of cranial nerve paralysis or visual field defect, with headache, suggests an intracranial aneurysm. If the meningeal syndrome appears, and if the spinal fluid is found to be bloody, the diagnosis is almost certain. Multiple sclerosis, brain tumors, and infections, such as cerebrospinal syphilis, should also be considered in the differential diagnosis. If the patient is seen several weeks or months after the attack, diagnostic difficulties may be increased. An expanding intracranial aneurysm, without rupture, will often be diagnosed as a cerebral neoplasm. Perhaps the most difficult problem of all is the differentiation from primary intracerebral hemorrhage. The history of previous rupture is of value. In cases of primary intracerebral hemorrhage the paralysis usually appears at the onset. In cases of ruptured aneurysm and extension of the bleeding intracerebrally, paralysis of the extremities is sometimes delayed. When the patients are unconscious and have bloody spinal fluid and a stiff neck, the correct diagnosis may not be possible.

A bruit is rarely heard over these aneurysms. Roentgenograms of the skull usually show nothing abnormal. Arteriographic examination of the cerebral vessels offers some hope of ascertaining the exact location of some of these lesions, but will often be disappointing in the case of the smaller aneurysms.

PROGNOSIS

In general, the prognosis is not good. Admittedly, in most of the cases which we have seen the disease was most severe. It is possible that a small defect in a vessel wall may heal without further trouble. However, if the patient survives one attack he is likely to have others. The immediate prognosis will often be in doubt. Decerebrate rigidity, a rising temperature, and the persistence of gross blood in the spinal fluid are ominous signs. The mortality is higher in older persons and in those who have arterial hypertension.

TREATMENT

The treatment of meningeal hemorrhage caused by ruptured intracranial aneurysm is principally symptomatic. Absolute rest in bed and analgesics are ordinarily recommended. Unusual exertion should be interdicted, and the patient should be kept in bed several weeks or more, depending upon how quickly his symptoms abate. The use of glucose intravenously is of questionable value in relieving the headache or

modifying the other symptoms. The question whether repeated spinal punctures should be done invariably comes up for consideration. From the diagnostic standpoint, spinal puncture is indicated. Occasional examination of the cerebrospinal fluid may be necessary to ascertain whether there is persistent bleeding; we have no evidence that spinal puncture is definitely harmful, or that repeated spinal drainage is of therapeutic value. In recent years neurosurgical procedures have been successfully utilized in the treatment of some of these patients. It is often difficult to locate the source of the bleeding, even when arteriographic examination is utilized.

CONCLUSIONS

The term "spontaneous subarachnoid hemorrhage" implies lack of knowledge concerning the cause of nontraumatic subarachnoid bleeding. In most of these cases, rupture of an aneurysm of the circle of Willis or its immediately adjacent branches is the source of the hemorrhage.

This study is based on the observation of 64 patients. In this group, the presence of an aneurysm was verified by post-mortem examination in twelve instances. The etiologic factors commonly given are congenital weakness of vessel walls, arteriosclerosis, inflammation, and trauma. We feel that long-standing structural weakness of the vessel wall, plus the mechanical factors induced at bifurcations, offers the most logical explanation for the majority of these aneurysms.

This is fundamentally a disorder of middle adult life, although bleeding may occur at any age. The most consistent symptom is sudden onset of pain in the head. The symptoms and signs of meningeal irritation make their appearance soon afterward. The presence of blood in the spinal fluid is a valuable aid in diagnosis.

Case reports are included to show variations in the clinical manifestations. Of the 64 patients examined, 18 died in the hospital, 22 were discharged well, and 24 were improved, but were left with sequelae such as hemiplegia, ocular palsy, aphasia, and visual field disturbances.

The prognosis must be guarded in every case. Recurrences often take place. The mortality is higher in older people and in patients who have arterial hypertension.

The treatment is principally symptomatic. Rest in bed and sedatives are necessary during the acute phase. Avoidance of undue excitement is indicated. Repeated lumbar punctures are of doubtful efficacy. Some of the patients with large, localizable aneurysms can be improved or cured by surgical means.

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ELECTROCARDIOGRAPHIC CONSIDERATIONS IN SMALL ANIMAL INVESTIGATIONS

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INTRODUCTION

THERE have been several investigations in which the electrocardiograph has been used to study cardiac changes in small animals subjected to abnormal dietary conditions. Agduhr and Stenström[1] attempted to relate the electrocardiographic pattern to pathologic changes which resulted from feeding cod-liver oil to mice. Weiss, Haynes, and Zoll[2] studied the cardiac rate, electrocardiographic complexes, and the response of rats to drugs in repeatedly induced states of vitamin B_1 deficiency.

In one of our investigations, the electrocardiographic method was contemplated for use in the study of cardiac changes in rats and mice infected with *Trichinella spiralis*. We found, however, that the usual electrocardiographic apparatus was not adequate because of the exceedingly rapid heart rates of mice and rats. This report is, therefore, preliminary to further investigation in which electrocardiographic principles may be applied in small animal experimentation, such as experimental trichinosis, Chagas's disease, sarcosporidiosis, bacterial myocarditis, and vitamin B_1 deficiency.

PRELIMINARY OBSERVATIONS

Electrocardiograms were taken on white mice with a commercial amplifier type of electrocardiograph.† Typical mouse electrocardiograms obtained with this apparatus are shown in Fig. 1. Measurements of the electrocardiograms showed that the time of rise of the R waves was less than the galvanometric speed. From an electrical standpoint it is well known that any galvanometer which possesses an inherent speed which is less than the electrical impulse that is being graphically recorded must introduce distortion. The electrocardiographic tests were repeated with Einthoven string galvanometer electrocardiographs, and the same form of distortion was noted (Fig. 2). Similar distortion was also noticeable in the records taken by the authors mentioned in the introduction to this article.

To prove the assumption that distortion is present and that it is a function of galvanometric speed, an electronic electrocardiograph was

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constructed, in which the galvanometric speed was adjustable, and a series of electrocardiograms was taken on each mouse at progressively increasing speeds. A few series of such tests immediately showed that the electrocardiographic pattern of each mouse underwent a gradual change as the galvanometric speed was progressively increased. Furthermore, the electrocardiographic configuration at high string speed was entirely different from that at usual electrocardiographic string speeds (Fig. 3). The electrocardiograms of Fig. 3 were taken on the same mice as those of Fig. 2.

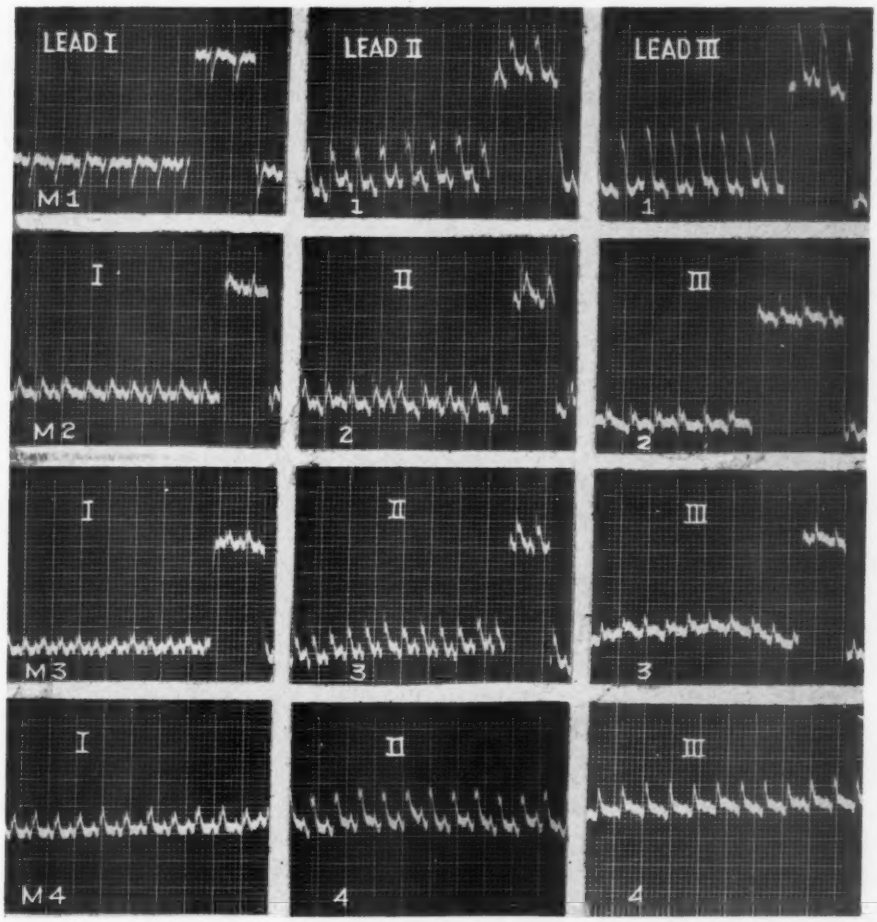

Fig. 1.—Typical appearance of four white mouse electrocardiograms obtained with a commercial amplifier-type electrocardiograph. The film speed is 50 mm. per second. The fine time lines are spaced 0.02 second and heavy time lines are spaced 0.10 second. The galvanometric speed is 0.01 second. The sensitivity is 2 cm. per millivolt.

ELECTROCARDIOGRAPHIC CONSIDERATIONS

The Theoretically Perfect Galvanometer.—When an electrocardiograph is standardized and the standardization is registered, a graph such as

that in Fig. 4, *A* should be recorded if the galvanometer is theoretically perfect. AB represents the isoelectric line. At point B, the millivolt standardizing potential is applied, and the galvanometer deflects one centimeter in zero time to point C. For the duration of the millivolt application, the galvanometer beam remains one centimeter above the isoelectric line. When the millivolt is removed at point D, the galvanometer beam drops to its original isoelectric level (EF) in zero time.

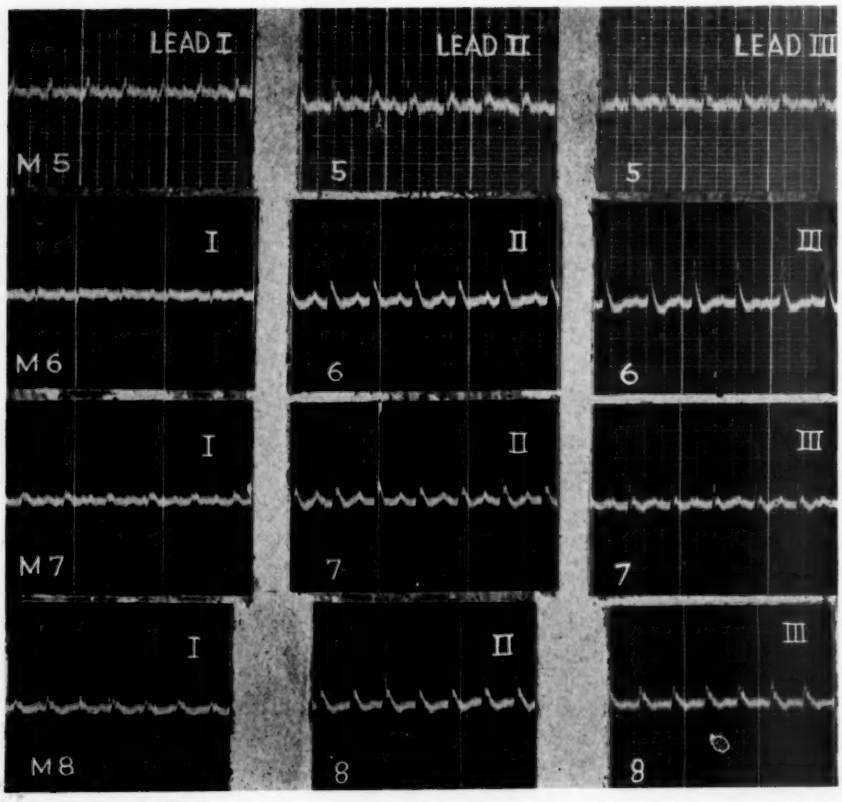

Fig. 2.—Typical appearance of four other white mouse electrocardiograms obtained with an Einthoven string galvanometer electrocardiograph. The film speed is 75 mm. per second, the fine time lines are spaced 0.04 second, and the heavy time lines are spaced 0.20 second. The string speed is approximately 0.01 second.

A galvanometer which produces a standardization curve such as that in Fig. 4, *A*, with angles ABC, BCD, CDE, and DEF perfect right angles, is capable of registering high speed (short duration) and low speed (long duration) electrical phenomena with no discrimination. The instantaneous response of the galvanometer (in zero time) to the standardizing potential indicates that the galvanometer is capable of following the fastest waves without introducing distortion. Since the beam remains parallel to the isoelectric line while the millivolt is applied, extremely slow electrical phenomena may likewise be regis-

tered without distortion. All intermediate electrical waves must, accordingly, be accurately recorded.

The Einthoven String Electrocardiograph.—An Einthoven string galvanometer electrocardiograph does not reproduce the theoretically perfect standardization curve under normal operating conditions. Any moving mass (such as a string) requires a definite amount of time to travel the distance BC or DE (Fig. 4, *A*). An Einthoven string electrocardiograph under normal operating conditions registers a standardization curve similar to Fig. 4, *B*. Angles ABC, BCD, CDE, and DEF are not right angles because the galvanometer beam consumes time *t* in traversing the distance BC or DE.

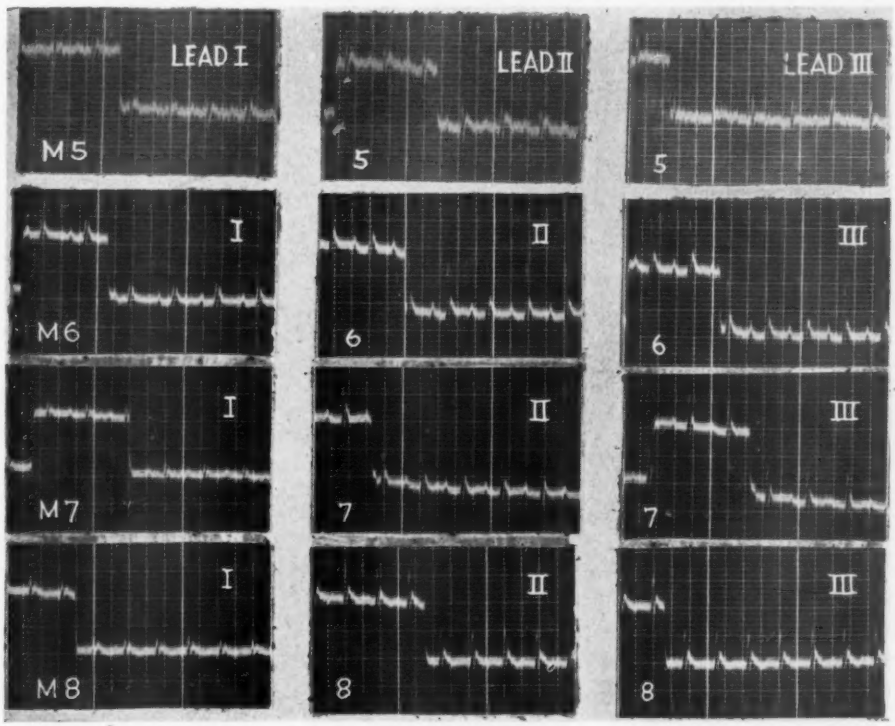

Fig. 3.—Electrocardiograms which illustrate how the white mouse electrocardiographic configuration is altered at high galvanometric speed as compared to the usual electrocardiographic string speeds. The records of Fig. 3 were taken on the same mice as those of Fig. 2. The high and low speed records on each mouse were taken within a few minutes of each other. The string speed is approximately 0.0015 second.

In an Einthoven galvanometer, the string tension is adjustable. The more taut the string, the higher is the natural vibratory period. A string of higher natural period consumes less time in traversing the distance BC or DE (Fig. 4, *B*) than at a lower natural period. Thus, as the string is drawn taut, the standardization curve approaches more closely the theoretically perfect curve of Fig. 4, *A*.

When the string tension is increased, the sensitivity is decreased; all Einthoven string electrocardiographs employ this principle for sensitivity control. Also, as the string tension is increased, the speed of the string is increased. Therefore, when an electrocardiograph is standardized so that a one centimeter deflection occurs when a millivolt is applied to the patient-galvanometer circuit, the tension of the string is thereby automatically selected. The constants of the galvanometer plus the resistance of the subject predetermine the speed of the string for a fixed value of sensitivity. An average commercial Einthoven string electrocardiograph, to which a subject with a "patient resistance" of about 2,000 ohms is connected, possesses a string speed of approximately 0.01 second. That is, the time *t* of Fig. 4, *B* is equal to approximately 0.01 second.

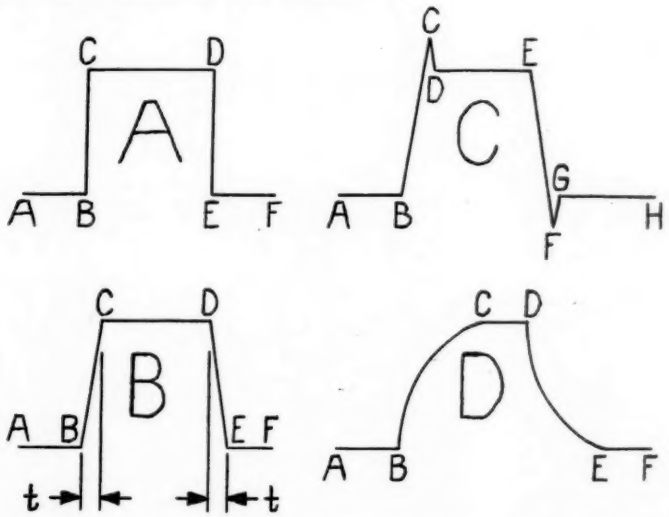

Fig. 4.—Einthoven string galvanometer standardization pulses.

The speed of an Einthoven string is directly dependent upon the resistance of the subject connected to it. When the subject resistance is more than 2,000 ohms, the string requires a time interval greater than 0.01 second to traverse the distance BC (Fig. 4, *B*). In man, a "patient resistance" of 2,000 ohms is a reasonable average value. Seldom does it fall below about 1,000 ohms, and, in some persons, a "patient resistance" of several thousand ohms is not uncommon. In small animals, the resistance is usually well in excess of 2,000 ohms unless extreme care is taken to keep the resistance low.

A factor of utmost importance is the degree of damping to which the string is subjected. In Fig. 4, *A* or Fig. 4, *B*, when the millivolt was applied at point B, the string traveled the one centimeter distance BC and came to a stop at C. All strings possess a definite mass, and, when set in motion, tend to remain so even after the activating stim-

ulus is removed. Unless something intervenes to prevent the string from overshooting its point of destination, a standardization curve such as that in Fig. 4, *C* is registered.

In commercial string electrocardiographs which employ a circuit resistance of a few thousand ohms (resistance of string plus "patient resistance"), overshooting at normal string tension is prevented by air friction, and, to a slight degree, by electromagnetic damping.[3] The effectiveness of electromagnetic damping as compared to air friction damping is so small that the former may be omitted in this discussion. The Einthoven galvanometer for electrocardiographic application must be so designed that at normal sensitivity (1 centimeter deflection per millivolt), with a "patient resistance" of approximately 2,000 ohms, the adjustment of the string is such that no overshooting takes place, and the string speed is approximately 0.01 second, or faster. This condition of damping must be fulfilled over a considerable range of string tension (above and below the optimum resonance value) for minimal distortion.

When a subject with a "patient resistance" considerably higher than 2,000 ohms is connected to the electrocardiograph, the string must be slackened to obtain the standard sensitivity of one centimeter deflection per millivolt. As a result, the speed of the string is decreased but the air friction is unaltered. The amount of air friction required to bring a loose string to a stop is less than for a taut string; this may result in an overdamped standardization curve (Fig. 4, *D*).

Electrocardiograms obtained with apparatus which produces standardization curves which are underdamped or overdamped are very likely distorted. Overshooting or underdamping tends to distort the electrocardiogram by increasing the amplitude of the fast initial deflections. Overdamping tends to decrease the amplitude of the fast deflections and slurs the faster electrocardiographic waves.

A standardization curve of any Einthoven string electrocardiograph indicates whether the apparatus is capable of registering an electrocardiogram accurately if:

1. The damping is critical; more than slight overdamping or underdamping is not permissible.
2. The string speed is not slower than 0.02 second (after Lewis and Gilder[4] *for human electrocardiographic applications*).
3. During the application of the standardization pulse of one millivolt, the string shadow deflects and remains deflected one centimeter.

Another source of distortion when the Einthoven string electrocardiograph is used is polarization effects[5] if improper electrode technique is employed. The distortion caused by polarization appears in a form similar to that of the underdamped string or overshooting.

The Electronic Booster.—The galvanometric speed of an Einthoven string electrocardiograph is limited. Slight improvements may be made by increasing the optical magnification and the magnetic field strength and by modifying a few other galvanometric factors. The loss of photographic definition and the disproportionate increase in the size of the magnetic structure which inevitably result from such procedure is definitely not compensated for by the slight gain in string speed.

When a galvanometric speed much faster than 0.01 second is desired for electrocardiographic work, the most economical and simplest procedure is to employ an electronic booster, or amplifier, in conjunction with a high natural period galvanometer. The galvanometer may be in the form of an Einthoven galvanometer whose string is drawn very taut; a reduction in the string length also increases the natural period. To attain extremely high speeds, both procedures may be necessary.

High natural period, "moving coil," or "moving vane" galvanometers may be substituted for the Einthoven galvanometer if an electronic booster is employed; these galvanometers are commonly referred to as "mirror" or "rotating mirror" galvanometers.[3] Most commercial amplifier electrocardiographs are of the "rotating mirror" variety. For the ultimate in galvanometric speed, the cathode ray oscillograph,[3] which employs a moving beam of electrons, may be used.

Two types of electronic amplifiers may be employed for electrocardiographic purposes, namely, the resistance-capacity coupled, and the direct coupled.[6] In a direct coupled amplifier, the electrical waves during the process of amplification pass through resistances and electronic tubes only. In the resistance-capacity coupled amplifier, the electrical waves pass through resistances, condensers, and electronic tubes. When a direct coupled amplifier is used, the operating characteristics of the electrocardiographic system are identical with that of the Einthoven system except that the galvanometric speed may be made much higher. The direct coupled amplifier may be considered as an adjunct to the optical system and the magnetic structure of the galvanometer, i.e., as an electronic magnifier for obtaining greater sensitivity to compensate for the loss in sensitivity when the galvanometric speed is increased.

A detailed technical discussion of direct coupled amplifiers which are suitable as electrocardiographic boosters is somewhat beyond the scope of this paper. It should, however, be mentioned that a direct coupled amplifier electrocardiograph is capable of producing a standardization curve similar to that of Fig. 4, *B*. The time element t may be considerably reduced by using either a fast Einthoven string galvanometer or a high natural period "mirror" galvanometer. The effects of "patient resistance" are eliminated for reasons which will be discussed later. Skin currents or potentials must be compensated for as is done in an Einthoven string electrocardiograph.

A reason for not using the direct coupled booster for electrocardiographic work is its characteristic instability. Direct coupled amplifiers with sufficient sensitivity to respond to one millivolt impulses usually exhibit this property. The resistance-capacity coupled amplifier, on the other hand, is a stable and reliable device, but possesses certain inherent characteristics which are somewhat different from that of the direct coupled amplifier and Einthoven string electrocardiograph. These dissimilar characteristics, however, are not a detriment, but a decided electrocardiographic asset, if properly controlled.

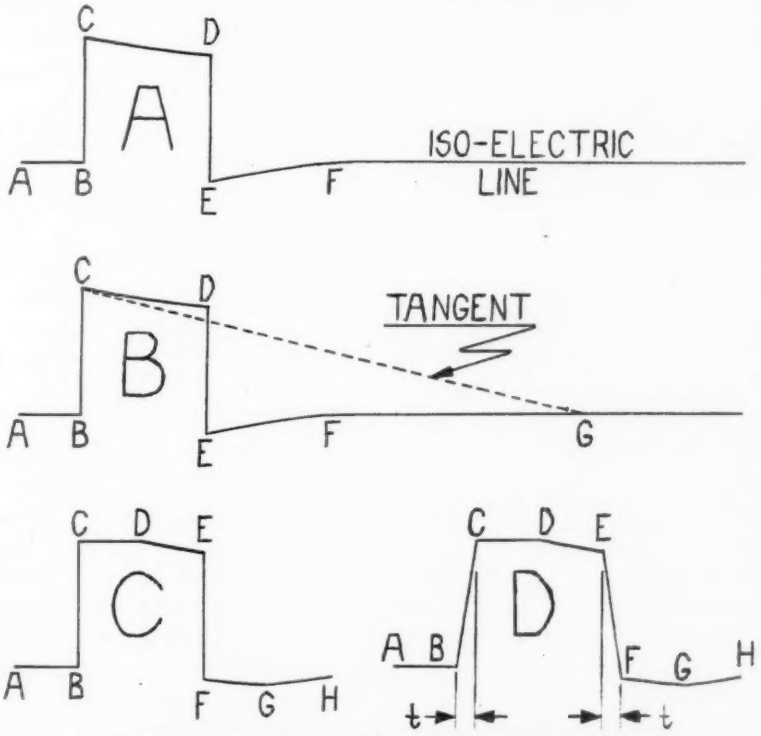

Fig. 5.—Resistance-capacity coupled amplifier standardization pulses.

If an infinitely fast galvanometer could be constructed which consumed zero time in traversing one centimeter when a millivolt was applied, and if the galvanometer were driven by a resistance-capacity coupled amplifier, a standardization curve similar to that shown in Fig. 5, *A* would be registered. AB represents the isoelectric line. At point B the millivolt standardizing potential is applied and the galvanometer deflects one centimeter in zero time to point C. From point C, the standardization is unlike that of an Einthoven string electrocardiograph in that the galvanometer beam does not remain one centimeter above the isoelectric line but tends to approach it at a logarithmic rate. That is, if the millivolt is applied for a considerable period, the galvanometer beam eventually drops to the level of the isoelectric line.

The logarithmic decrement is caused by the resistance-capacity coupled amplifier. In this type of amplifier, when the millivolt is applied, the condensers in the circuit become charged and then discharge through the associated resistors. The rate of decay may be controlled by means of the resistors and condensers. The larger the resistors and condensers, the slower is the rate of decay.

When the millivolt is removed at point D, the galvanometer beam drops exactly one centimeter below point D to point E, which is somewhat below the isoelectric line. The distance point E falls below the isoelectric line depends upon the time of application of the millivolt, as is obvious from the figure. From point E, the beam gradually drifts back to the level of the isoelectric line. Line EF is also logarithmic and similar to line CD.

Schwartzchild and Kissin[7] ascertained the relationship of decay rate to electrocardiographic accuracy. They found that if a tangent CG is drawn (Fig. 5, *B*) to the logarithmic decrement CD at point C, and if the duration of BG is two seconds or more, the apparatus is suitable for clinical purposes. Theoretically, the greater the duration of BG, the more accurate is the electrocardiograph in the registration of low frequency or slow cardiac changes.

Miller,[8] by a modification of the electronic circuit, succeeded in producing a standardization curve which resembles that of Fig. 5, *C*. After the initial millivolt deflection, the beam is parallel to the isoelectric line for approximately 0.1 to 0.2 second (represented by CD), and then commences to decay logarithmically to point E, where the millivolt is removed. The beam immediately deflects one centimeter (represented by EF). Point F falls below the isoelectric level a distance equal to the logarithmic decay that has taken place (represented by DE). FG is a continuation of the logarithmic curve DE, but displaced one centimeter. At point G the beam commences to return to the isoelectric level. If the millivolt were removed before point D was reached, no logarithmic decay would have taken place. In such a case, the beam would drop exactly to the isoelectric line.

The purpose of the Miller circuit is to reproduce the Einthoven string electrocardiograph type of standardization and retain the advantages of the resistance-capacity coupled amplifier. For a period of about 0.1 to 0.2 second after the millivolt is applied, conditions are exactly similar to that of the Einthoven string electrocardiograph for the registration of slow phenomena. There is no known electrocardiographic wave which has a constant potential duration in excess of 0.1 second. Therefore, any slow electrocardiographic wave must register accurately when the standardization possesses a flat top for a period of 0.1 second or more.

As in the Einthoven string electrocardiograph, the moving element of the galvanometer requires a definite amount of time to traverse the one centimeter when a millivolt is applied. Therefore, the actual standardization should appear as in Fig. 5, *D*, where the deflection time

of the galvanometer is represented by the interval t. Although the theoretically perfect condition of zero time deflection cannot be achieved with an amplifier and high speed galvanometer, it may be approached. Especially does this hold true if a cathode ray oscillograph is used.

As the galvanometric speed is increased, the amplifier must be made more powerful and, in turn, is more costly. From an economic standpoint, it is not worth while to employ galvanometric speeds in excess of electrocardiographic requirements. We found that a galvanometric speed of approximately 0.0015 second is ample for registering the fastest electrocardiographic complexes that may be found in a mammal as small as the white mouse, whose average normal heart rate is approximately 750 per minute, and under abnormal conditions, when the rate may be higher.

The only animal, to our knowledge, with a heart rate more rapid than that of the white mouse is the humming bird, with a rate of approximately 1,000 per minute. The electrocardiographic requirements for accurate registration of normal and abnormal cardiac action potentials of humming birds were not considered because the humming bird is not an experimental laboratory animal.

Skin potentials may reach a value as high as 50 millivolts. Superimposed upon the skin potential are the pulsating cardiac action potentials. A resistance-capacity coupled amplifier electrocardiograph is capable of automatically eliminating the effects of the nonpulsating skin potentials. In small animal work, automatic skin potential compensation is desirable because it is more difficult to keep the string within the camera limits than in human applications.

Automatic skin potential compensation in the resistance-capacity coupled electrocardiograph is accomplished in the following manner: when a subject is connected to the electrocardiograph, the galvanometer beam deflects in proportion to the magnitude of the skin potential and then drifts back at a logarithmic rate to the level of the isoelectric line; meanwhile, the beam keeps pulsating in proportion to the cardiac action potentials that are being generated.

When an electrocardiogram is taken with an Einthoven string electrocardiograph, the machine must be recalibrated for each lead; when an electronic booster is used, recalibration with each lead is not necessary. This is advantageous in animal work. An understanding of the underlying theory should be of interest.

When a subject is connected to an Einthoven string electrocardiograph, the heart may be considered as a generator with the "patient resistance" and string connected in series with it (Fig. 6). The amount of current that can flow through the string, according to Ohm's law, is equal to the voltage generated by the heart at any instant, divided by the sum of the "patient resistance" and "string resistance." Therefore, according to Ohm's law, the higher the value of the "patient resistance," the less is the cardiac current that can flow

through the string; a decrease in cardiac current flow through the string in turn produces a proportionate decrease in string deflection. Thus, with a 2,000 ohm string and a possible difference of several hundred ohms between leads, the percentage change in electrocardiographic sensitivity may be considerable. For example, if the "patient resistance" is 2,000 ohms, the string resistance is 2,000 ohms, and the instantaneous cardiac action potential is one millivolt, the instantaneous current through the string, according to Ohm's law, is

$$\frac{0.001}{2{,}000 + 2{,}000} = 0.25 \text{ microampere.}$$

Should the "patient resistance" in another lead be 4,000 ohms, the instantaneous current in the string would be

$$\frac{0.001}{4{,}000 + 2{,}000} = 0.16 \text{ microampere.}$$

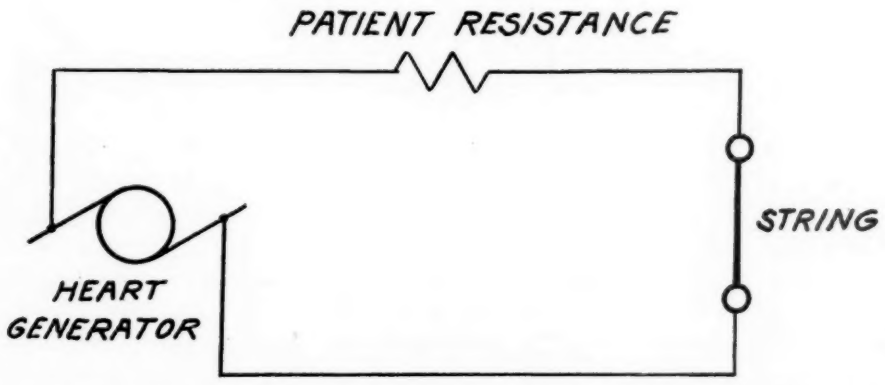

Fig. 6.—Schematic of electrical components to illustrate the relationship of the heart as a generator, and the consideration that must be given the "patient resistance" and the "string resistance."

If the string was adjusted to deflect one centimeter per millivolt with the 2,000 ohm lead, as is normally done in electrocardiography, the substitution of a 4,000 ohm lead would produce a deflection of 0.64 centimeter instead of the required one centimeter. To compensate for the loss in sensitivity in the latter lead, the string must be made more slack.

In an amplifier electrocardiograph (direct coupled or resistance-capacity coupled), the patient is connected across a resistance in the grid circuit of the amplifier (Fig. 7). The grid resistor may possess a value of several million ohms. If we apply Ohm's law to the resulting patient circuit, we find that, with a 2,000-ohm patient, a 10 million ohm grid resistor, and an instantaneous cardiac action potential of one millivolt, the instantaneous current which flows through the grid resistor is $\frac{0.001}{2{,}000 + 10{,}000{,}000}$ ampere, whereas, with a 4,000 ohm patient, the instantaneous current is $\frac{0.001}{4{,}000 + 10{,}000{,}000}$ ampere. The

amount of current that flows through the grid resistor controls the deflection of the electrocardiographic beam for a fixed setting of the sensitivity control. Therefore, a difference of several thousand ohms in "patient resistance" can merely alter the current through the grid resistor by an insignificant percentage for equal values of instantaneous cardiac potential. Therein lies the reason why an amplifier type electrocardiograph with a high input resistance may be standardized initially and any combination of leads registered thereafter without readjusting the sensitivity.

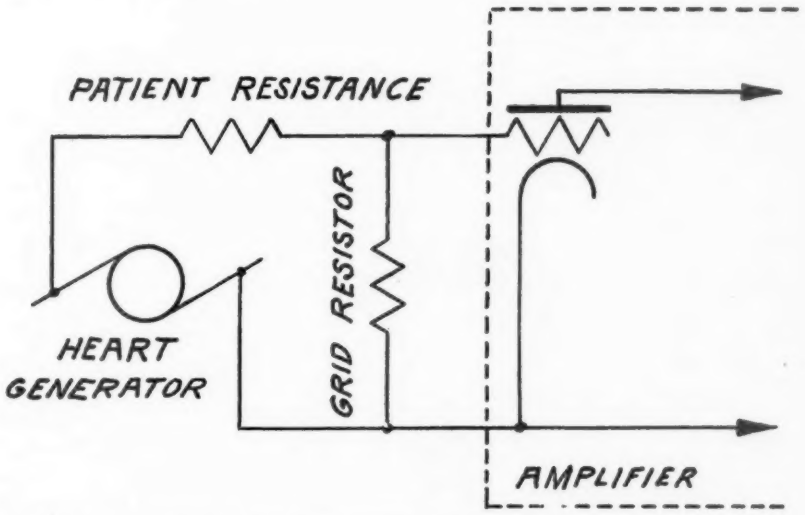

Fig. 7.—Schematic of the input circuit of an amplifier electrocardiograph.

In an electronic electrocardiograph, the speed of the galvanometer may be permanently set. Unlike the Einthoven electrocardiograph, in which the sensitivity is controlled by adjusting the string tension, and, in turn, the string speed, the sensitivity of the electronic electrocardiograph is adjusted by means of a control in the amplifier which adjusts the degree of amplification, and, in turn, only the electrocardiographic sensitivity. As a result, the characteristics of the galvanometer in the electronic electrocardiograph are unaltered under all possible sensitivity settings.

The Experimental Apparatus.—Fig. 8 shows the electrical circuit of the resistance-capacity coupled amplifier which was used in conjunction with an Einthoven string electrocardiograph. By varying the string tension, the galvanometric speed was adjustable between the limits of less than 0.01 second and approximately 0.0015 second.

A description of the booster follows: A standard three limb patient cable such as is used on all electrocardiographs connects with a lead selector switch with four positions: Standardize, and Leads I, II, and III. The lead selector switch is followed by a three stage

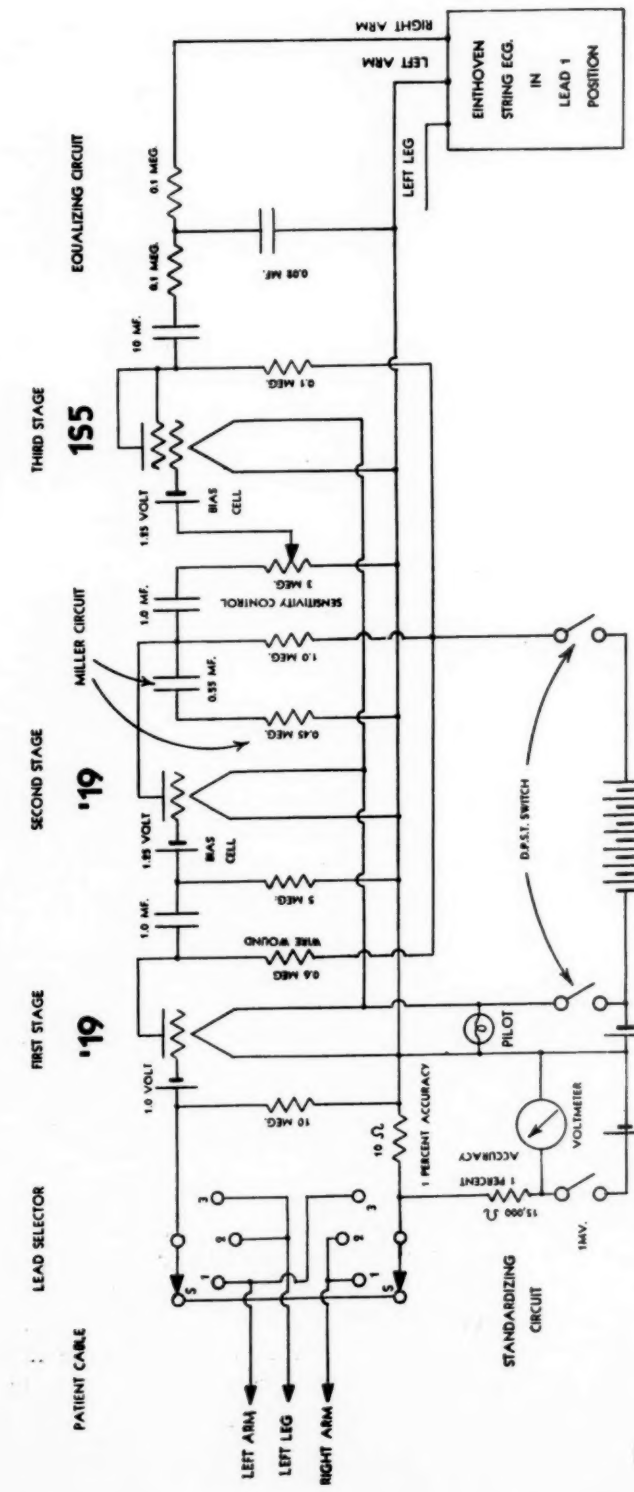

Fig. 8.—Wiring diagram of an electronic booster which may be used with an Einthoven string electrocardiograph for small animal work.

resistance-capacity coupled amplifier. The first and second stages are triodes contained in the type '19 tube; the third stage is a 1S5 tube wired as a triode. Between the third stage and the Einthoven string electrocardiograph is an equalizing circuit to critically damp the string. That is, when a string is drawn more taut than the customary electrocardiographic tension, air friction damping is inadequate to prevent the string from overshooting. As a result, an equalizing circuit must be added. The Miller corrective network for producing a flat top standardization is located in the plate circuit of the second stage. The standardization circuit for producing a millivolt pulse is located at the input of the amplifier, i.e., between the lead selector switch and the grid circuit of the first stage.

When constructing the resistance-capacity coupled booster, the following should be kept in mind:

1. In the Miller corrective network, the 0.45 megohm resistor may have to be varied slightly in order to obtain the flat top standardization curve. Once this adjustment is made, it does not have to be altered during the life of the apparatus.

2. If string speeds well in excess of 0.0015 second are desired, the equalizing circuit shown in Fig. 8 may be inadequate; in such a case, a resonant shunt damping circuit[3] must be substituted.

3. In the standardization circuit, an ordinary 1.5 volt dry cell may be used. Because the drain is negligible, and lasts only for very short periods, while the millivolt switch is depressed, the cell will maintain its voltage within electrocardiographic measuring accuracy for at least six months of its shelf life. The voltmeter indicates whether the voltage of the cell is within required limits.

4. The entire amplifier, plus batteries, must be built into a metal case to eliminate the possible pickup of stray alternating current disturbances. The metal case must be electrically connected to the magnet structure or ground circuit of the Einthoven string electrocardiograph.

5. It is advisable to support the amplifier unit on soft rubber pads in order to eliminate mechanical disturbances.

6. String centering and protection are accomplished by means of the usual controls in the Einthoven electrocardiograph.

Technique.—The unanesthetized mouse is tied in a supine position to a board (Fig. 9). The same procedure is also applicable to the larger laboratory animals. The four paws are first tied to the nails on the wood block. Electrode jelly is then applied to the right and left fore paws and the left hind paw. The electrode consists merely of a fine copper wire twisted around the paws (approximately four turns) over the areas to which the electrode jelly had been applied. (In some instances, pin electrodes were used instead of the jelly and wire.) The patient cable of the amplifier is then connected to the spring clips so that the "right arm" corresponds to the right fore

paw, the "left arm" to the left fore paw, and "left leg" to the left hind paw.

Subject resistance does not affect the accuracy of the electrocardiogram when an amplifier type electrocardiograph is used. However, the higher the subject resistance, the greater is the likelihood of picking up alternating current disturbances of an electrostatic nature.

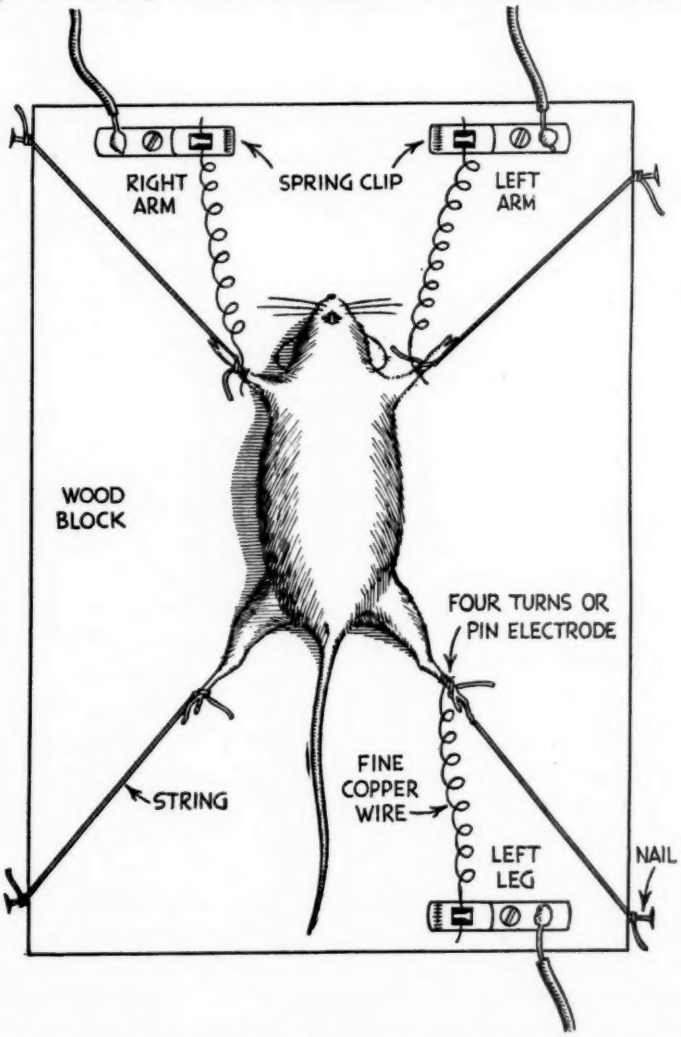

Fig. 9.—Diagram showing manner in which a small animal, such as a mouse, may be connected to an electrocardiograph.

Therefore, in locations where alternating current wiring and apparatus are present, more care should be taken to keep the subject resistance low.

Recordings of the three standard leads were taken both with and without the amplifier. The interval between the two sets of recordings

was very short, i.e., merely the time required to make the necessary adjustments. The animal during this interval was not disturbed.

We found that it is generally desirable to allow the animal to remain in position and undisturbed for several minutes after all adjustments are made to it before registering the electrocardiogram. As a general rule, the animal will quiet down sufficiently to allow the taking of satisfactory electrocardiograms. After mice have been subjected to this treatment several times, they become less excitable and more cooperative.

Electrocardiographic Observations.—Seldom are white mouse electrocardiograms completely free of somatic tremor when taken with an electrocardiograph which possesses a high galvanometric speed, although the mouse may have appeared relaxed; at usual galvanometric speeds, the electrocardiograms are usually free of somatic tremor when the same technique is used. As the galvanometric speed is gradually increased, the presence of somatic tremor in the electrocardiogram becomes more evident. This indicates that somatic tremor in a mouse is of a comparatively high frequency. As the galvanometric sensitivity to the higher frequencies is increased, the somatic tremor components register with increased amplitude. The frequency of the major components of the tremor lies between approximately 200 and 1,000 cycles per second.

When white mouse electrocardiograms are taken at the usual galvanometric speeds of approximately 0.01 second (Figs. 1 and 2), they show a distinct P wave. The QR interval is usually less than the galvanometric speed. What appears to be the RS interval is, as a general rule notched; below the notch, the complex appears slurred. No T wave is seen. The electrocardiogram, as a whole, does not resemble those from larger animals.

On the other hand, when high galvanometric speeds of 0.0015 second or more are employed on the same mice (Fig. 3), the electrocardiogram does resemble that of a larger animal in many respects. A P wave is present. The QR interval is of longer duration than the galvanometric speed. A distinct and normal appearing QRS complex is present. A distinct S wave is present in at least one of the three leads of each mouse. The T wave occurs rather soon after the S wave, and in most normal mice it appears in continuity with the S wave.

The average commercial electrocardiograph is designed primarily for human application. In small animal work the electrocardiographic requirements are more exacting because of the high cardiac rates and short duration of some of the complexes. Thus, when an electrocardiogram is taken with an average commercial electrocardiograph which possesses a galvanometric speed not much in excess of 0.01 second, several forms of distortion may be introduced.

The most obvious electrocardiographic distortion in the white mouse is in the general appearance of the QRS and T waves. As was previ-

ously mentioned, if the galvanometric speed is slower than the electrical phenomenon that is being graphically recorded, the electrical phenomenon will register inaccurately. The duration of the QR interval in the average normal mouse is considerably less than 0.01 second. As a result, the graphic representation of the QR segment is incorrect in a slow system. Also, the cardiac action potential which stimulates the galvanometer terminates before the galvanometer has had a chance to traverse the required distance. The result is an amplitude attenuation of the QRS registration.

Likewise, the RS segment is distorted if the galvanometric speed is too slow. That is, the electrocardiographic registration lags behind the action potential, and the action potential terminates before the recording beam or shadow has traversed the true distance. The T wave which follows immediately registers as a notch on the RS segment, well above the isoelectric line. The slurring effect is actually part of the T wave. The S wave must obviously be absent. Also, because the slopes of the fast waves are incorrectly registered, the duration of a fast wave, such as R, must register incorrectly.

Because of the fact that the electrocardiographic complexes do not register with the correct slope and amplitude when the galvanometric speed is too slow, phase distortion is introduced. That is, the time intervals between electrocardiographic complexes are reproduced incorrectly because the slow waves register correctly and the fast waves appear displaced from their true location.

SUMMARY AND CONCLUSIONS

1. A theoretically perfect galvanometer for electrocardiographic work produces a standardization wave which is a perfect rectangle. That is, zero time is consumed by the galvanometer in traversing the one centimeter deflection, and during the application of the millivolt the beam is parallel to the isoelectric line, but displaced one centimeter.

2. An Einthoven string galvanometer electrocardiograph cannot reproduce the theoretically perfect standardization curve because any moving mass, such as a string, requires a definite amount of time to traverse the one centimeter distance when the millivolt is applied. The resultant standardization curve must therefore resemble a trapezoid.

3. In an Einthoven galvanometer, the string tension is adjustable. The more taut the string, the higher is its natural vibratory period. A string of higher natural period consumes less time in traversing the one centimeter distance when the millivolt standardizing pulse is applied than one with a lower natural period.

4. When the string tension is increased, the sensitivity is decreased; all Einthoven string electrocardiographs employ this principle for sensitivity control. Also, as the string tension is increased, the speed of the string is increased. Therefore, when an electrocardiograph is standardized so that a one centimeter deflection occurs when a milli-

volt is applied, the tension of the string is automatically selected. The constants of the galvanometer plus the resistance of the subject predetermine the speed of the string for a fixed value of sensitivity.

5. A factor of utmost importance is the degree of damping to which the string is subjected. Overdamping or underdamping tends to distort the electrocardiogram.

6. The standardization curve of any Einthoven string electrocardiograph indicates whether the apparatus is capable of registering an electrocardiogram accurately.

7. Electrocardiographic distortion caused by polarization effects may occur if improper electrode technique is employed.

8. The galvanometric speed of an Einthoven string electrocardiograph is limited. When a galvanometric speed much faster than about 0.01 second is desired for electrocardiographic work, the most economical and simplest procedure is to employ an electronic booster or amplifier in conjunction with a high natural period galvanometer.

9. Two types of electronic amplifiers may be employed for electrocardiographic purposes, namely, the resistance-capacity coupled and the direct coupled. The resistance-capacity coupled amplifier is the better of the two.

10. The theoretically perfect standardization curve of a resistance-capacity coupled amplifier type electrocardiograph is not exactly similar to that of the theoretically perfect Einthoven electrocardiograph. For approximately the first 0.1 to 0.2 second after the millivolt is applied, conditions are exactly similar to the Einthoven system, but, thereafter, a logarithmic decrement sets in until the beam reaches the isoelectric line.

11. Although the theoretically perfect condition, under which the beam will deflect one centimeter in zero time when a millivolt is applied, cannot be achieved even with an amplifier type electrocardiograph, this perfect condition may be approached more closely.

12. As the galvanometric speed is increased, the amplifier must be made more powerful and, in turn, more costly. From an economic standpoint, it is not preferable to employ galvanometric speeds in excess of electrocardiographic requirements.

13. A galvanometric speed of approximately 0.0015 second is ample for registering the fastest electrocardiographic complexes that may be found in a mammal as small as the white mouse, whose average normal heart rate is approximately 750 beats per minute.

14. A resistance-capacity coupled amplifier type electrocardiograph is capable of automatically compensating the subject's skin potentials. An Einthoven string electrocardiograph requires a manually operated compensation control. The logarithmic decay characteristic which is common to all resistance-capacity coupled amplifier electrocardiographs accomplishes the automatic skin potential compensation.

15. When an electrocardiogram is taken with an Einthoven string electrocardiograph, the machine must be recalibrated for each lead; the amplifier coupled electrocardiograph does not require recalibration with each lead.

16. In an electronic electrocardiograph the speed of the galvanometer may be permanently set. Unlike the Einthoven electrocardiograph, in which the sensitivity is controlled by adjusting the string tension and, in turn, the string speed, the sensitivity of the electronic electrocardiograph is adjusted by means of a control in the amplifier which adjusts the degree of amplification and, in turn, only the electrocardiographic sensitivity.

17. The constructional features of a resistance-capacity coupled amplifier that may be used with a commercial Einthoven string electrocardiograph for small animal work are given.

18. The technique for small animal electrocardiography is described.

19. The theoretical aspects of distortion in small animal electrocardiography are discussed. Experimental proof is given that average commercial electrocardiographs (both Einthoven string and amplifier types) are incapable of registering the cardiac action potentials of small animals with any degree of accuracy. Commercial electrocardiographs are designed primarily for human application, where the requirements are not so severe.

20. The accurate recording of electrocardiographic complexes, as described herein, makes possible further investigations in which electrocardiographic principles may be applied in small animal experimentation.

We wish to express our appreciation for the cooperation of the Sanborn Company, of Cambridge, Massachusetts, in this investigation. We are also grateful for the constructive criticisms of Dr. Paul D. White, of the Massachusetts General Hospital.

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THE PROGNOSTIC SIGNIFICANCE OF AGE AT ONSET IN INITIAL ATTACKS OF RHEUMATIC FEVER

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ALTHOUGH there is difference of opinion regarding the seriousness of the prognosis in rheumatic fever at different ages within childhood,[1-4] it is generally accepted that the disease is more serious and more likely to lead to cardiac damage in children than in adults. This conclusion has had support from a number of investigations, most of which have been based on long-term observations on groups of patients over a number of years. Obviously, however, estimation of the significance of age at onset in these long-term studies is complicated by the important fact that repeated attacks have occurred in many of the patients but not in others. This difficulty can be obviated by limiting one's analysis to the results of initial attacks only, and this has been done by several observers. Church,[5] in a study of 244 first attacks, found that 75 per cent of the patients under 10 years of age developed signs of cardiac damage, but that this figure diminished progressively to 12.5 per cent in those who developed first attacks after 40 years of age. Mackie[6] found cardiac involvement in 74 per cent of 112 patients under 15 years of age, and in 38.3 per cent of 107 patients over 25 years of age. Similar differences between children and adults with initial attacks of rheumatic fever were reported from Australia by Sangster,[7] who found persisting evidence of cardiac damage at the time of discharge from the hospital in 40 per cent of children under 12 years of age and in 25 per cent of patients over that age. Reports limited to children have been made by Sutton and Dodge[8] and Ash.[9] The former studied 66 children in their first attacks of rheumatic polyarthritis, and noted carditis in 40.9 per cent and persisting evidence of heart disease at the time of discharge from the hospital in 27.3 per cent. In Ash's group of 297 children with polyarthritis, 60 per cent were considered to have organic valvular disease at the termination of the initial attack.

In studying the incidence of cardiac damage in rheumatic fever one is interested in knowing, first, whether the heart is involved during the attack, and, second, whether the damage resulting from that involvement is sufficient to cause clinically recognizable, persistent, organic heart disease. In none of the reports mentioned above were both of these analyzed for both children and adults, and this study was undertaken for that purpose.

All patients studied were from the Third (New York University)

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Medical Division and the Children's Medical Service* of Bellevue Hospital. The cases reviewed from the adult service covered the period 1920 to 1937, and those from the children's service, the period 1930 to 1937. The children were 12 years old or less, and the adults over 25 years; the interval from 12 to 25 years was omitted in order to insure a distinct separation of the two groups. Originally, we had intended to include all types of rheumatic manifestations in the analysis, but chorea and carditis without joint involvement were so infrequently encountered during first attacks in the adults that polyarthritis was the only manifestation which could be used for comparison of the two age groups.

Cardiac damage was divided into the two categories previously mentioned: (1) carditis during the attack of rheumatic fever, and (2) the development of pathologic changes in the heart sufficient to lead to signs of persisting organic heart disease at the termination of the rheumatic activity. The criteria for making a diagnosis of carditis were the appearance while under observation of one or several of the following in a patient with rheumatic fever: (1) Diastolic murmurs with or without cardiac enlargement, or systolic murmurs with enlargement, (2) significant electrocardiographic changes,† (3) gallop,‡ (4) precordial pain and tenderness, (5) significant arrhythmias, (6) disproportionate tachycardia,‡ and (7) pericardial friction rub or effusion. The criteria for persisting organic heart disease were the presence of diastolic murmurs or of systolic murmurs plus cardiac enlargement at the time of discharge from the hospital, after all evidence of active carditis and all other manifestations of active rheumatic fever had disappeared. To insure accuracy of interpretation, all patients with an unreliable or uncertain previous history or with indications of possible cardiac involvement prior to admission were excluded. Because of the strictness of the requirements, it is probable that some cases of mild rheumatic fever with low-grade carditis which could not be diagnosed with certainty were excluded. However, by employing uniform criteria for the inclusion of adults and children we believe that accurate comparisons have been attained.

RESULTS

The results of this comparison are shown in Table I. Of 67 adults with an initial attack of frank polyarthritis, 30 per cent developed cardi-

TABLE I

CARDIAC DAMAGE IN CHILDREN AND ADULTS WITH INITIAL ATTACKS OF RHEUMATIC POLYARTHRITIS

AGE	NUMBER OF PATIENTS	INCIDENCE OF CARDITIS		INCIDENCE OF PERSISTING CARDIAC DAMAGE	
		NUMBER	PER CENT	NUMBER	PER CENT
Under 12 years	78	36	46	22	28
Over 25 years	67	20	30	5	7

*Many of the children had been included in the report of Sutton and Dodge.[8]

†In addition to the frank arrhythmias, the changes accepted as significant were prolongation of the P-R interval and the changes associated with pericarditis.

‡These were accepted as indicative of carditis only when accompanied by other signs.

tis during the attack, but only 7 per cent showed physical signs of cardiac damage at the time of discharge from the hospital. Among the 78 children studied, the incidence of carditis was 46 per cent, and evidence of persisting cardiac damage on discharge was present in 28 per cent, or four times as often as in the adults. Thus, in this series of patients, not only was carditis less frequent in adults than in children, but also it was much less serious when it did occur.

DISCUSSION

It must be emphasized that our figures are for first attacks only, and that the incidence of cardiac damage in these patients undoubtedly increased as new attacks of rheumatic fever were incurred with the passing years. They do, however, indicate a distinct difference in the incidence and degree of cardiac damage in the two age groups studied. In this connection, it should be noted that our figures had to be derived from study of a single rheumatic manifestation, polyarthritis, because of the infrequency of other manifestations in initial attacks among the adults. This is of practical significance to our study, for it is well established that some rheumatic manifestations have more serious prognostic import than others. Thus, when carditis occurs alone or with subcutaneous nodules, it is more likely to be followed by serious cardiac damage than is polyarthritis, whereas chorea has a very much less grave significance.[8, 10, 11, 12] Therefore, although polyarthritis was the only manifestation compared for the two age groups, we also noted the incidence of cardiac damage in (1) the entire group of children with first attacks, (2) those with all manifestations excluding chorea, and (3) those with chorea alone. As is shown in Table II, both carditis and persisting physical signs of cardiac damage at discharge were less frequent in the children with chorea than in the adults with polyarthritis (Table I). When chorea was excluded, on the other hand, the incidence of carditis and persisting cardiac damage rose sharply. Even when chorea was included, the incidence of cardiac damage was higher than in our group of adults with polyarthritis.

Although the groups were small, we were interested to learn the frequency of fatal terminations in these first attacks of rheumatic fever. None of the 67 adults died, but there were four deaths among the 263 children, or 1.5 per cent; and if the 151 patients with chorea were ex-

TABLE II

INCIDENCE OF CARDIAC DAMAGE DURING INITIAL ATTACKS OF VARIOUS RHEUMATIC MANIFESTATIONS IN CHILDREN

TYPE OF MANIFESTATION	NUMBER OF CHILDREN	INCIDENCE OF CARDITIS		INCIDENCE OF PERSISTING CARDIAC DAMAGE	
		NUMBER	PER CENT	NUMBER	PER CENT
All manifestations combined	263	79	30	54	21
All manifestations, excluding chorea	112	64	57	45	40
Chorea alone	151	15	10	9	6

cluded, the mortality rose to 3.6 per cent. Among the 78 children with polyarthritis, one (1.3 per cent) died; whereas, among twelve who had subcutaneous nodules, three (25 per cent) died. This high mortality in the children with nodules is in agreement with the accepted view regarding their serious prognostic significance, but in this connection it must be noted that three of the surviving children with nodules left the hospital with no physical signs of cardiac damage, although they did have carditis during the height of the illness. Of course, severe carditis was present in all the fatal cases. These figures are in conformity with the usual clinical opinion regarding fatality in initial attacks of rheumatic fever.

Finally, it must be emphasized that the relatively low incidence of serious cardiac damage suffered by the adults of our series does not warrant a lessening of vigilance in the care of this age group. This is especially true in the case of adults whose hearts have already sustained damage in earlier attacks of rheumatic fever, for it is our belief that in these patients further cardiac damage almost invariably results.

SUMMARY

A clinical analysis was made of the incidence of cardiac damage during initial attacks of rheumatic fever. The data presented indicate that first attacks of rheumatic polyarthritis are less likely to be accompanied by clinically evident carditis in adults than in children, and that when carditis does occur it is very much less likely to result in serious cardiac damage in the adults.

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THE TONGUE SIGN FOR HIGH VENOUS PRESSURE

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THE veins of the undersurface of the tongue are admirably situated for observation. In the average person they are 8 inches, or 200 mm., above the right auricle, so that when the person is erect, or sitting, the veins are collapsed unless the venous pressure is abnormally high, i.e., greater than 8 inches, or 200 mm. Normal venous pressure is 50 to 150 mm., or 3 to 5 inches, so that the level of the tongue veins is just in the region of elevated venous pressure.

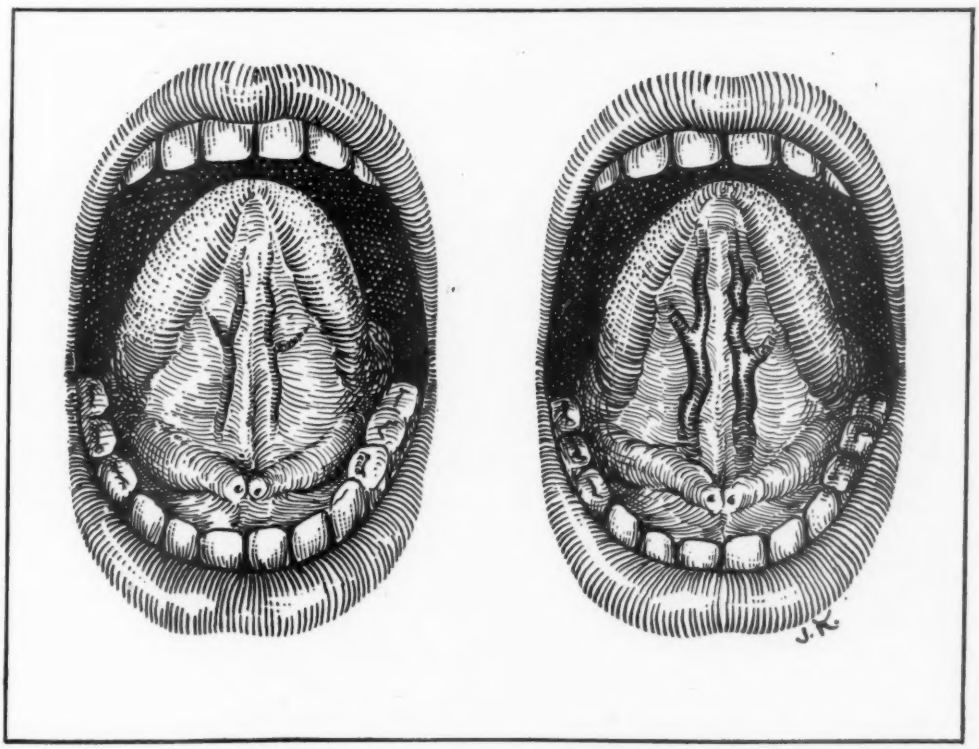

Fig. 1.

Clinically, we have found that this is a reliable sign of increased venous pressure, and one that is immediately obvious and certain. The dilation of the veins is unmistakable, and may be duplicated in the normal person by having him recline on a bed or couch.

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Clinical Reports

THE PHONOCARDIOGRAM IN SPONTANEOUS INTERSTITIAL EMPHYSEMA OF THE MEDIASTINUM

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THE sounds produced over the upper part of the precordium by spontaneous interstitial emphysema of the mediastinum and lung have intrigued the medical profession. Griffin[1] regards these "popping" or "crunching" sounds as diagnostic of this condition, and reported three cases with this sole thought in mind. Hamman,[2] who was the first to describe the condition (1937), also thought that these interesting physical signs are pathognomonic. The reports that followed Hamman's article[3] applied a variety of descriptive terms to the precordial sounds; bubbling, crunching, popping, and crackling were those most frequently employed. The following case is reported because of the interesting phonocardiograms which were taken shortly after the occurrence of spontaneous mediastinal emphysema. To our knowledge, it is the first phonocardiogram in this condition to be reported.

REPORT OF A CASE

C. F., a 28-year-old white man, was admitted to Cedars of Lebanon Hospital Aug. 14, 1942, with a complaint of severe substernal pain of one and one-half hours' duration. The patient was an employee of the hospital ambulance company, and his work entailed lifting three to five patients a day. He was in excellent health until approximately ninety minutes before admission to the hospital, at which time, about an hour after having lifted a patient, he developed moderate substernal distress which radiated into his left arm to the elbow. He left his ambulance and helped lift another patient, but on the way to the hospital the pain became so severe that he told his partner he was afraid he could not help remove the patient. In about fifteen minutes the pain had attained terrific proportions, so that he lay back in his seat, became pale, and refused to move. Deep respirations were especially painful. He was seen shortly after arriving at the hospital. His blood pressure at that time was 130/90, his pulse rate, 90, and his respiratory rate, 30. Morphine sulfate in a dose of ¼ grain was given in the ambulance, and the man was removed to the ward.

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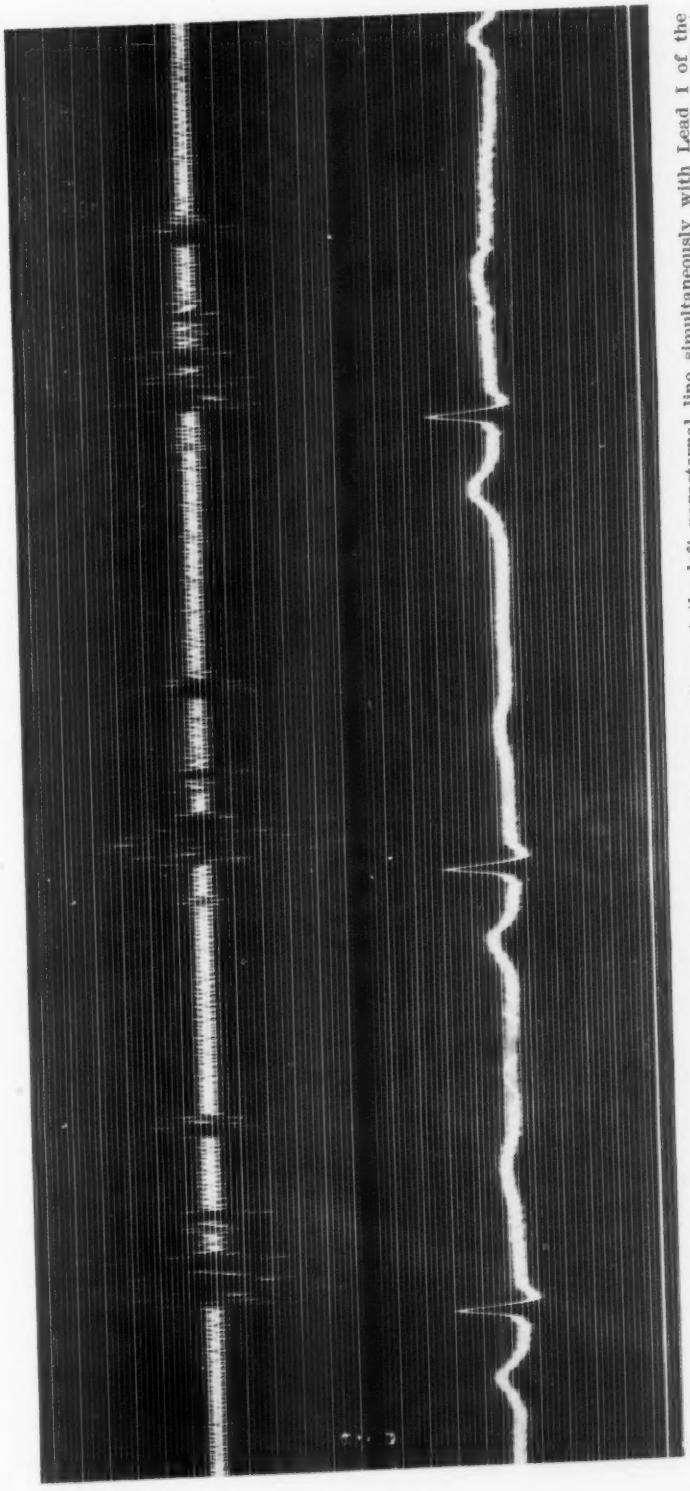

Fig. 14.—Stethogram taken at the onset of the illness, over the precordium at the left parasternal line simultaneously with Lead I of the electrocardiogram. A large diaphragm bell was employed. Note the prolonged systole of varying intensity and pitch. There is also a slight presystolic bruit.

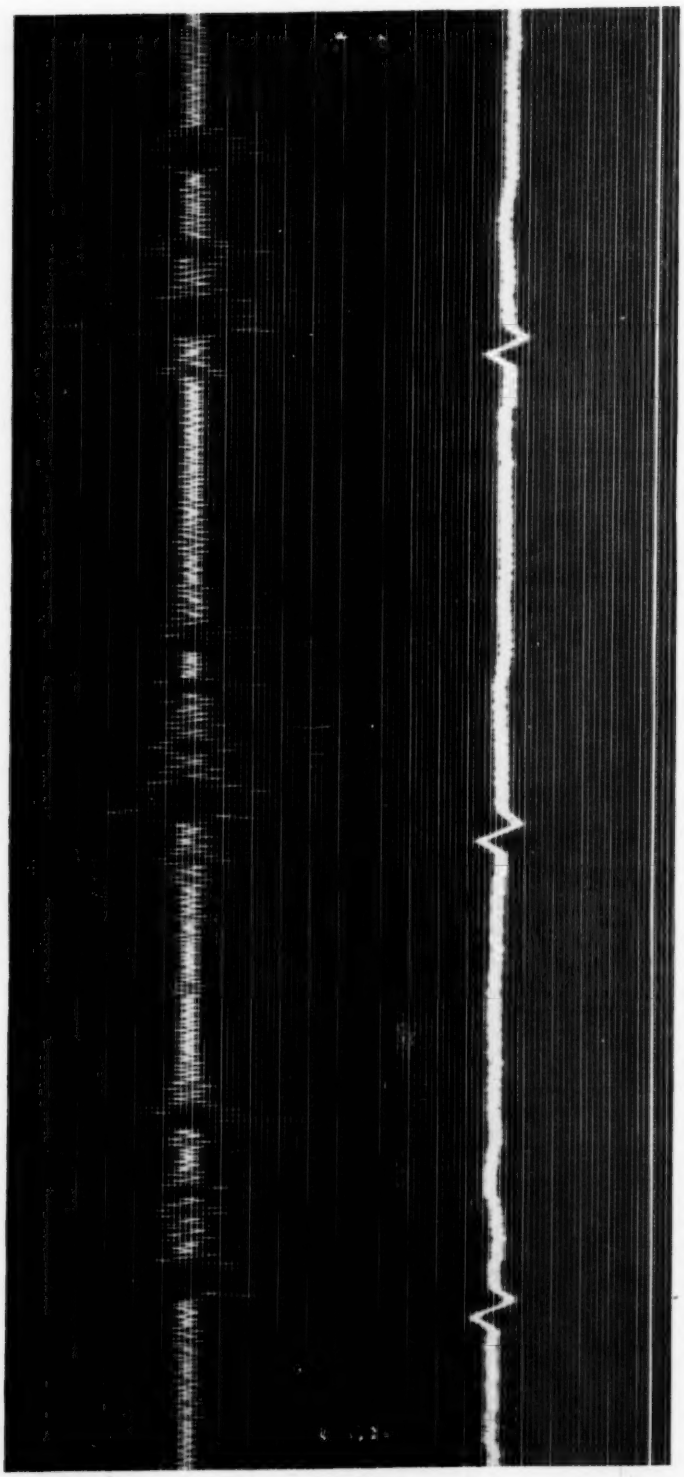

Fig. 1*B*.—Simultaneous electrocardiogram-stethogram taken in same area with Lead II and a large open bell.

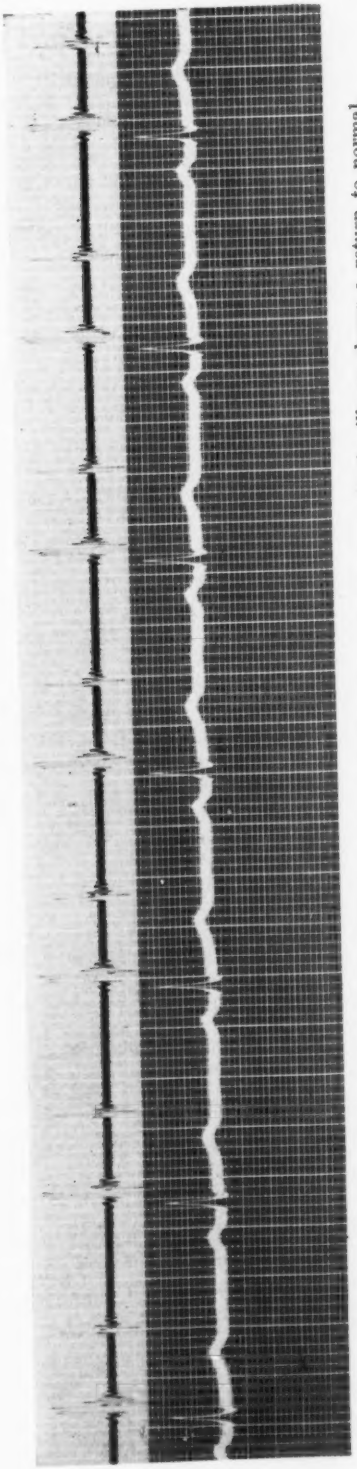

Fig. 2.—Simultaneous electrocardiogram-stethogram taken twelve days after the onset of the illness shows a return to normal.

Past History.—The patient had had inflammatory rheumatism at the age of 8 years. He was ill for one and one-half years at that time. His heart had been examined repeatedly thereafter, but no evidence of disease was reported. There was no history of tuberculosis or asthma. The family history was negative.

Physical examination revealed a white man who was lying comfortably in bed, smiling, and even laughing, and in no apparent distress—forty-five minutes to an hour after receiving ¼ grain of morphine sulfate. The blood pressure was 120/80, the pulse rate, 80, and the respiratory rate, 25 per minute. Physical examination was essentially negative except for the heart. There was resonance to 1 inch to the left of the sternum. Over the apex of the heart a remarkable sound was heard. It was a crunching, popping, knocking bruit, synchronous with the heart beat, and was heard best on deep expiration when the patient was lying on the left side. No subcutaneous emphysema developed. Expansion of the chest was limited, and the percussion note was not abnormal.

The hemoglobin was 96 per cent, the erythrocyte count, 5,000,300, and the leucocyte count, 9,500. The sedimentation rate was 12 mm. in 258 minutes. The blood Wassermann reaction was negative. The urine was normal. An electrocardiogram on August 14 showed an auricular and ventricular rate of 90, sinus rhythm, and normal A-V conduction time. Lead I showed low voltage of the R wave; Lead II showed low voltage of the QRS complex and upright T and P waves; Lead III showed low voltage of QRS, a small R wave, and an upright T wave; and Lead IV showed a small R wave and an upright T wave. A roentgenogram of the chest, August 14, showed that the heart was of comparatively normal shape, size, and position. The arch and descending aorta were also of normal shape and size. The hila were somewhat increased in size and density. The root branches were accentuated. There was a partial pneumothorax at the left apex. An electrocardiogram which was made August 17 was identical with that of August 14.

A phonocardiogram was taken on the day after admission and is reproduced in Figs. 1*A*, 1*B*, and 2. The pain decreased gradually. The day after admission he no longer needed opiates, his temperature varied between 97 and 98.8° F., his pulse rate remained constant between 70 and 80, and his respiratory rate was about 20. The precordial bruit decreased in intensity, and, on August 18, four days after its onset, it could scarcely be heard. The patient was always comfortable, and his only complaint after cessation of the sudden, severe pain on admission was that of discomfort on deep inspiration.

SUMMARY

A case of spontaneous mediastinal emphysema is reported. Phonocardiograms showed that the peculiar sounds produced by the air in the mediastinum were synchronous with each cardiac impulse and occurred regularly with each systolic contraction.

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ANEURYSM OF THE PULMONARY ARTERY

Report of a Case in Which the Aneurysm Apparently Developed Under Observation

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Honolulu, Hawaii

ANEURYSM of the pulmonary artery is rare. According to Scott,[1] both Ambroise Paré and Lancisi observed cases. Boyd and McGavack[2] reviewed the literature from 1833 to 1939, and discovered 111 cases in which the diagnosis was proved by autopsy. Since their paper was published, ten articles on the subject have been listed in the Quarterly Cumulative Index Medicus.[3a-j] In the case which follows, probably the one hundred twenty-fourth to be reported, an aneurysm of the pulmonary artery apparently developed while the patient was under observation.

CASE REPORT

The patient, a 12-year-old Filipino girl, had been under observation at the Palama Settlement Medical Clinic since the age of 6 years because of cardiac enlargement and a family history of tuberculosis. During this six-year period, various descriptions of her cardiac abnormalities were recorded. In 1937 it was stated: "Heart enlarged outside nipple line one inch. No edema. Harsh systolic murmur loudest in the pulmonary area." A roentgenogram of the chest at that time was said to have shown cardiac enlargement and no evidence of tuberculosis. In 1939 a systolic thrill was present in the second left intercostal space. There were repeated statements regarding her poorly nourished appearance. Cyanosis and clubbed fingers were not observed at any time.

On March 11, 1942, the patient came to the Palama Clinic complaining of a painful right foot. There was no history of injury. A small reddish spot was present on the sole of her right foot. It was noted that there was no history of rheumatic fever and that a congenital cardiac lesion was to be considered. The record stated: "The lesion on the foot may be embolic." A roentgenogram of the chest showed cardiac enlargement (Fig. 1). She returned to the Clinic three weeks later, complaining of dyspnea after mild exertion. The foot lesion had disappeared. Her temperature was 98.8° F., and the physical signs were as noted above. She was again brought to the Clinic in May, after having been kept at home in bed for three weeks because of fever. Her temperature was 102.2° F., and her pulse rate was 116. Sulfathiazole was ordered in a dose of 3 Gm. daily for six days, but her response to this therapy is unknown because she did not return to the Clinic as directed.

The patient was first examined by one of us on July 3, 1942, after

From the Palama Settlement Medical Department and the Kauikeolani Children's Hospital.
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she had coughed up a small amount of bright red blood. Examination revealed an emaciated, underdeveloped, dyspneic, 12-year-old girl. There was no cyanosis or clubbing of the fingers. The skin was pale, and coarse hyperkeratoses were present over the back and chest. Arterial pulsations were prominent in the neck. Marked bronchial breathing was present at the left base posteriorly. The heart was enlarged to the left. Gallop rhythm was present at the apex, and a loud systolic murmur was noticed in the second left intercostal space, with a thrill in systole. No diastolic murmurs were found. The abdomen was moderately distended, and the spleen and other organs were not palpated. The extremities were thin and the reflexes were normal.

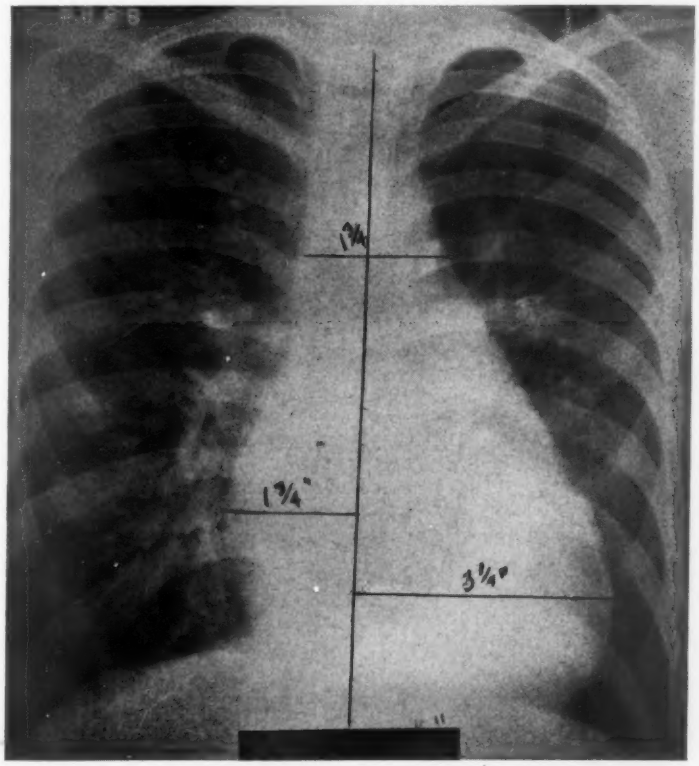


Fig. 1.—Roentgenogram taken March 11, 1942, four months before death.

Fluoroscopic examination of the chest showed marked prominence of the pulmonary conus area and vascular congestion. Otherwise, the lungs were normal. Both ventricles were greatly enlarged. Examination with barium showed no esophageal displacement.

Impression: Patency of the ductus arteriosus; malnutrition; subacute bacterial endocarditis?

She was referred to the Kauikeolani Children's Hospital.

During the patient's twelve-day hospital stay her temperature varied from 99 to 101° F., and her pulse rate was consistently around 110. Dyspnea persisted, and she coughed up small amounts of blood occasionally. Her erythrocytes numbered 2,750,000 per cu. mm., and her

hemoglobin (Dare) was 50 per cent. Her leucocytes numbered 13,200 per cu. mm., and a differential count showed 92 per cent polymorphonuclear granular leucocytes and 7 per cent lymphocytes. Polychromatophilia and marked anisocytosis were observed. The urine contained no sugar, 1 plus albumin, and 4 to 5 leucocytes and occasional erythrocytes per high-power field. Three sputum examinations showed no acid-fast organisms. Two blood cultures were taken, and both were positive for *Streptococcus viridans*. She was given 7½ grains of sulfathiazole every four hours, and the usual supportive measures were taken.

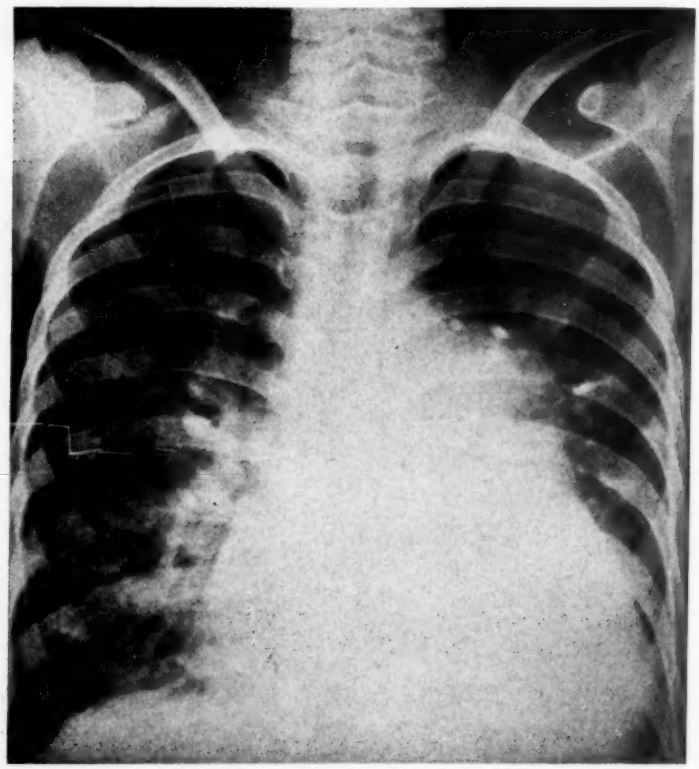


Fig. 2.—Roentgenogram taken July 13, 1942, two days before death. Note the changed appearance of the pulmonary conus area.

A roentgenogram of the chest revealed cardiac enlargment and marked prominence in the pulmonary conus area (Fig. 2). This was not present four months before (Fig. 1). On the tenth hospital day the patient complained of sharp pain in the right lower part of the chest, and coughed up small amounts of bright red blood. Two days later, upon awakening, she appeared to be quite weak and refused breakfast. A short time later she suddenly gasped for breath and died within a few minutes.

NECROPSY (SIGNIFICANT ABNORMALITIES)

The body was emaciated. No free fluid was present in the peritoneal cavity. The left pleural cavity was entirely obliterated by old ad-

hesions. The right lower pulmonary lobe was firmly attached to the chest wall by both old and recent adhesions. Both lungs were subcrepitant to noncrepitant throughout, and were deep purple in color. Both, upon sectioning, presented multiple infarcts of various sizes, several of which were broken down centrally. The intervening lung parenchyma was edematous and congested, although no areas of pneumonic consolidation were observed. Several calcified nodes were present near the left hilum, the largest of which measured 1½ cm. in diameter.

The pericardial sac was filled with a large amount of blood clot and approximately 200 c.c. of serosanguineous fluid. An aneurysm about the size of a small lemon was found, arising from the anterior wall of the pulmonary artery just before its bifurcation. There was a recent linear tear, approximately 1 cm. in length, near the apex of the aneurysmal sac.

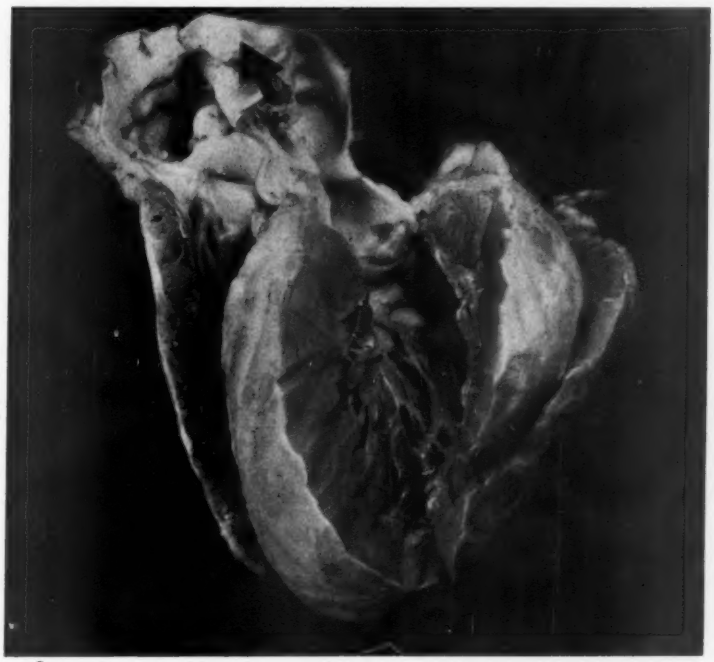


Fig. 3.—Arrow points to the patent ductus arteriosus. The aneurysm of the pulmonary artery is shown containing vegetations.

The heart was greatly enlarged (345 grams). The wall of the left ventricle measured 2 to 2½ cm. in thickness, and the muscle was firm and pale in color. The mitral valve ring measured 9 cm., and a number of small, discrete, friable vegetations were present several millimeters above the free margin of the valve. There were similar vegetations on the endocardium of the left auricle more than 1 cm. above the free edge of the valve. The tricuspid, aortic, and pulmonary valves were normal in appearance.

The aneurysmal sac measured 3½ cm. in diameter and 2½ cm. at its base, which was located approximately 2 cm. above the pulmonary

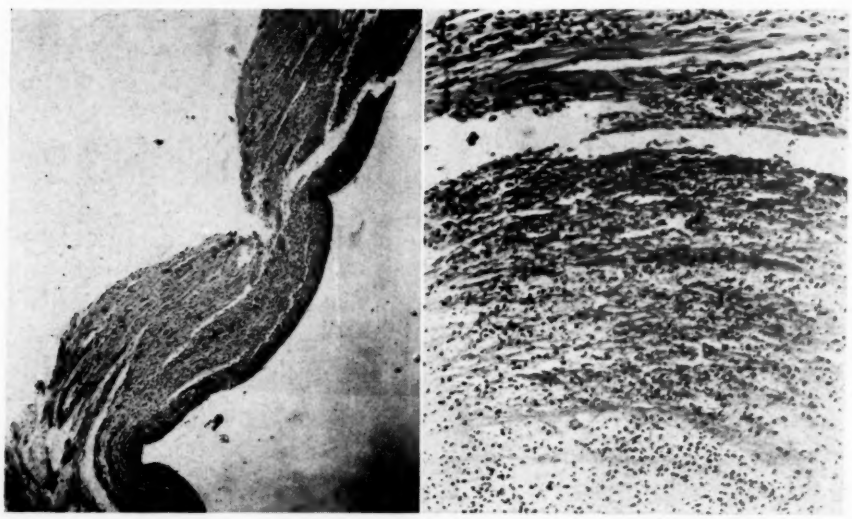
valve ring. The aneurysmal wall was extremely thin, almost "paper-thin" in certain areas, and at no point measured more than a few millimeters in thickness. Numerous friable vegetations were attached to the base of the aneurysm and to the endocardial portion of its wall, and these extended for a short distance along the intima of the pulmonary artery. They were generally quite small; the largest measured slightly less than 1 cm. in diameter.

Opposite the opening of the aneurysmal sac there was a large, patent ductus arteriosus which communicated with the aorta just before the origin of the great vessels from the arch (Fig. 3). It measured 1 cm. in diameter and possessed a smooth intima with no gross evidence of bacterial involvement.

The liver was moderately enlarged, and, upon sectioning, presented distinct vascular markings, i. e., the typical appearance of chronic passive congestion.

The spleen was enlarged and presented several firm, well-organized infarcts, the largest of which measured about 2 cm. in diameter.

The pancreas, adrenals, kidneys, pelvic organs, and gastrointestinal tract presented no gross abnormality.



A. *B.*

Fig. 4.—Section of the aneurysm wall. *A*, Showing a widespread, diffuse inflammatory reaction (×85); *B*, Same, ×260.

MICROSCOPIC STUDY

Examination of sections taken through the wall of the aneurysmal sac revealed widespread diffuse and focal inflammatory involvement (Fig. 4 *A* and *B*). The wall varied in thickness from place to place; generally, it was quite thin. The intima, for the most part, was entirely replaced by irregular patches of fibrin. Fibroblastic proliferation was prominent, and an interesting feature was the presence of miliary abscesses about the smaller blood vessels. Diffuse lymphocytic and plasma cell infiltration was present in most portions of the wall, and a generous sprinkling of polymorphonuclear granular leucocytes was observed. The cells mentioned above were concentrated about blood

vessels, many of which were newly formed, and consisted of a single layer of endothelium. Microscopic examination of the mitral valve showed moderate scarring, with hyalinization and loss of structure.

Patches of fibrosis were observed in sections taken through the left ventricle, and the individual muscle fibers were greatly hypertrophied. Many of the vessels were surrounded by cuffs of lymphocytes and mononuclear cells, but the histologic changes which are typically associated with rheumatic myocarditis were lacking.

Sections taken through the lungs revealed the changes associated with pulmonary infarcts of varying size and age; several of these exhibited tissue breakdown, and were characterized by the presence of acute cellular exudate in their central portions.

DISCUSSION

There is a strong possibility that the aneurysm of the pulmonary artery which ruptured and caused this patient's death was a fairly recent development in her illness. The roentgenogram which was taken four months prior to her death showed enlargement of the heart, but no prominence in the area of the pulmonary conus. In addition to the patent ductus, there may have been a small aneurysm of the pulmonary artery which could not be seen in an anteroposterior chest roentgenogram, but of that we have no proof. The prominence in the conus area, however, was most striking in the fluoroscopic examination, as well as in the roentgenogram taken after she entered the hospital.

About four months before death she began to have a fever, and suffered from a lesion which was most likely an embolism in the foot. Patients with uncomplicated patency of the ductus arteriosus commonly have an enlarged left ventricle,[4] and, when they develop a superimposed infection on the site of the ductus, emboli may lodge either in the lung or in the peripheral circulation. The mitral valve, as well as the patent ductus, was the seat of vegetation in this patient. The former area may have given rise to the peripheral embolism. She also had numerous pulmonary infarcts which most probably came from the ductus vegetations.

The possibility that such vegetations may extend to the pulmonary arterial wall, and weaken it so that an aneurysm results, is mentioned by Scott.[1] Sections of the aneurysm wall in our case (Fig. 4) showed evidence of bacterial infection. The probability that the infection caused the pulmonary arterial wall to weaken, so that an aneurysm occurred, is thus given strong support. Boyd and McGavack,[2] in their review of the literature and discussion of the 111 cases in which the diagnosis was confirmed at autopsy, state:

"Congenital anomalies were present in 66 per cent of the cases and were deemed important etiologic factors in 43.2 per cent. Unequal division of the truncus arteriosus was evident in at least six, and open ductus arteriosus in twenty-four (23 per cent). Although pulmonary hypertension occurs in cases of patent ductus arteriosus and has been

regarded as causative of aneurysm, patency of this passage is not uncommon without aneurysm. Accordingly, it seems reasonable to assume that some additional lesion, such as superimposed infection or atheromatosis, may contribute to the production of the aneurysm in this group."

SUMMARY

Aneurysm of the pulmonary artery is rare.

A case is presented in which the aneurysm apparently developed while the patient was under observation.

There is evidence which strongly suggests that, in this case, the superimposed bacterial infection played a prominent role in producing the aneurysm.

We wish to express our thanks to Dr. J. Lam and Dr. W. B. Herter for permission to present the case, and to The Queen's Hospital Photographic Department for the photographs.

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STAPHYLOCOCCUS AUREUS SEPTICEMIA, WITH OSTEOMYELITIS, PNEUMONIA, AND ACUTE PURULENT PERICARDITIS

Case Report

Captain Robert R. Impink, Medical Corps, Captain Eric Denhoff, Medical Corps, and Major Joseph B. VanderVeer, Medical Corps

THIS case history concerns a 4-year-old patient who was treated in an Army Evacuation Hospital on a semitropical island in the South Pacific area. The child was the victim of a fortuitous social condition, in that medical care on the part of local physicians was practically nonexistent because of the exigencies of the war. She, along with other ailing natives, was therefore forced to appeal to the American Army Medical Corps. The child suffered from a hemolytic *Staphylococcus aureus* septicemia, with secondary osteomyelitis of the right femur, acute purulent pericarditis, pneumonia, and pleurisy with effusion. Her apparently complete recovery is attributed to the combined use of chemotherapy and surgical treatment.

CASE REPORT

A 4-year-old Indigène girl, desperately ill, was brought to an Army Evacuation Hospital, May 23, 1942. Three days before admission she had fallen, and thereafter complained of pain in the right thigh. This pain increased in severity and made walking impossible. General malaise, chills, and fever developed. An officer of a field Army Medical Unit saw the child and noted fullness and tenderness in the right thigh. Suspecting a fracture, he brought the patient to the hospital for treatment.

The patient was the child of a white father, who was the son of an Australian settler, and a Melanesian mother.

Physical examination on admission revealed an extremely ill, malnourished native child, crying vociferously and striking and biting the attendants whenever the right thigh was manipulated. Dehydration was moderate. The temperature was 105° F., the pulse rate was 150, and the respiratory rate was 65. The lungs and heart were normal. An oval area, 3 by 6 cm., tender to palpation, was present on the anterolateral aspect of the right mid-thigh. No tenderness or swelling was noted in either the right hip or knee joint, although passive motion of both was restricted.

Roentgenograms of the pelvis and the right leg showed no abnormalities of the bones or joints. The erythrocyte count was 3,400,000, and the leucocyte count, 12,900; there were 67 per cent polymorphonuclear leucocytes, 6 per cent of which were juvenile. The urine contained a trace of albumin and 6 to 8 erythrocytes per high-power field.

From 52nd Evacuation Hospital, Colonel Ralph L. Cudlipp, Commanding; Lieutenant Colonel Henry P. Brown, Jr., Chief of Surgical Service.

Received for publication Dec. 7, 1942.

A diagnosis of acute hematogenous osteomyelitis of the right femur was made.

COURSE

Shortly after admission the child was given Ringer's solution parenterally, a transfusion of 65 c.c. of whole blood, and proctoclyses of 2 per cent sodium bicarbonate solution. The right femur was immobilized in a plaster of Paris hip spica in order to eliminate pain and facilitate nursing care. The administration of sulfathiazole in a dose of 1½ grains per pound of body weight per twenty-four hours was begun immediately. After twelve hours, sulfadiazine in the same dosage was substituted for the sulfathiazole. A blood culture which was taken shortly after admission was reported positive for *Staphylococcus aureus hemolyticus* in less than twenty-four hours. Multiple small transfusions were administered throughout the first week, as indicated on the chart (Fig. 2). During this period there was considerable improvement in her general condition, but lethargy, toxemia, and fever persisted.

On May 27, the fourth day after admission, the development of respiratory distress, a thready pulse of 176 per minute, a respiratory rate of 60 per minute, distended neck veins, and slight edema of the face and vulva suggested the presence of a complication. The cardiac dullness was found to be enlarged to percussion, the heart sounds were faint, and a pericardial friction rub was audible over the entire precordium. The administration of oxygen through a catheter in the nose was begun. On the following day there were physical signs of an area of consolidation in the upper lobe of the left lung. Examination of the right thigh through a window in the cast revealed more definite localization of the tenderness to the mid-shaft area, but no fluctuation. Another blood culture was positive. During the next few days there was slight improvement in the general condition, but edema of the face, extremities, and vulva became marked. Twitching and shaking of the head were traced to acute, bilateral otitis media. It was necessary to resort to gavage.

On May 31, eight days after admission, a roentgenogram of the chest showed considerable enlargement of the cardiac shadow (Fig. 1*A*). This was interpreted as probably due to cardiac dilatation, although pericardial effusion could not be ruled out. The pericardial friction rub persisted for several days, then gradually disappeared. A roentgenogram of the right femur showed periostitis of the mid-shaft area. Examination of the thigh on this date revealed an area of deep fluctuation. This was incised through a lateral approach, under local anesthesia. One hundred cubic centimeters of thick yellow pus were obtained. The abscess lay on the anterolateral aspect of the bone, and extended from the upper third of the shaft to a line just above the popliteal space. The bone had been denuded of periosteum in this area by the infectious process. After making a counterincision into the lower extremity of the cavity posteriorly, vaseline gauze packing was inserted and a plaster of Paris spica reapplied. On the following day the patient seemed much improved. *Staphylococcus aureus hemolyticus* was grown from a culture of pus taken from the abscess, and a blood culture taken just prior to operation showed the same organism. Because of this, bacteriophage, previously obtained through the courtesy of Dr. Ward MacNeal of the New York Postgraduate Hospital, was administered intravenously in increasing doses, beginning at 1:30 P.M. on June 1. There was no reaction

to this therapy, which was continued for one week. The maintenance dose of sulfadiazine was also continued during this period. The first blood culture to be reported negative was obtained on June 1, just before the bacteriophage therapy was initiated. With the subsidence of the blood stream infection the temperature became normal and the pulse and respiration rates diminished markedly. However, continuance of the septicemia was suggested by the appearance of multiple petechiae in the skin of the palms of the hands and beneath the nails of the fingers and toes. These lesions persisted for about one week. On June 6 the vaseline gauze was removed and reapplied more loosely into the abscess cavity of the thigh. A moderate amount of pus was present in the cavity as well as on the outer dressings. Because the edema had not regressed a plasma transfusion of 100 c.c. was given June 10. This was followed by diuresis. Sulfadiazine therapy was stopped on June 11 because the temperature was normal and an urticarial rash, which was suspected of being secondary to the drug, had developed.

In addition to edema of the face, extremities, and vulva, abdominal distention and hepatomegaly were noted on June 12. Examination of the heart revealed a marked increase in the area of cardiac dullness. The heart sounds were well heard with the patient in the semirecumbent position. Pulsus paradoxus was never noted. On June 14, aspiration of the pericardial sac yielded 110 c.c. of thin, cloudy, yellow fluid. Smears showed many pus cells, but no organisms. A culture of this material was negative. This tap and later ones were done in the fifth left intercostal space at approximately the anterior axillary line. The anasarca diminished at once, but a gradual rise in temperature followed. There were signs of pneumonitis in the left upper lobe. On June 17 the temperature reached 106° F., the pulse rate was 176, and the respiratory rate, 66 per minute. Sulfadiazine therapy was reinstituted. A roentgenogram of the chest showed marked enlargement of the cardiac shadow as a result of pericardial fluid, and also free fluid in the pleural cavity (Fig. 1*B*). On June 20, a thoracentesis was done, and 250 c.c. of thin, cloudy, yellow fluid were obtained. Culture of this fluid was negative. This was followed by improvement, as shown on the chart (Fig. 2). Sulfadiazine administration was discontinued June 27.

Because of recurrent generalized edema, a large tender liver, increasing cardiac dullness, and distant heart sounds the pericardial sac was aspirated a second time June 30, and 100 c.c. of cloudy fluid were obtained. Smears and culture of this fluid were negative. The child showed little change during the next ten days. A moderate degree of edema of the face and vulva and the large tender liver persisted. Two hundred twenty-five cubic centimeters of thin, cloudy, yellow fluid were removed July 12. Two days later a third pericardial tap yielded 175 c.c. of thin, purulent fluid (Fig. 1*C*). Smears of both these fluids showed many pus cells, but no organisms. The cultures were negative. After this last pericardial tap there was a rapid reaccumulation of fluid. The signs of elevated venous pressure did not subside after this aspiration, as they had previously. Consequently, during the week of July 19 three pericardial taps were performed, yielding 110 c.c., 50 c.c., and 60 c.c. of fluid, respectively. The fluid became thicker on each occasion, and could not be withdrawn completely. Despite the thick pus, smears showed no bacteria and the cultures were sterile. Because of lack of improvement in the general condition and the persistence of signs of cardiac failure, more adequate drainage of the pericardial space was essential.

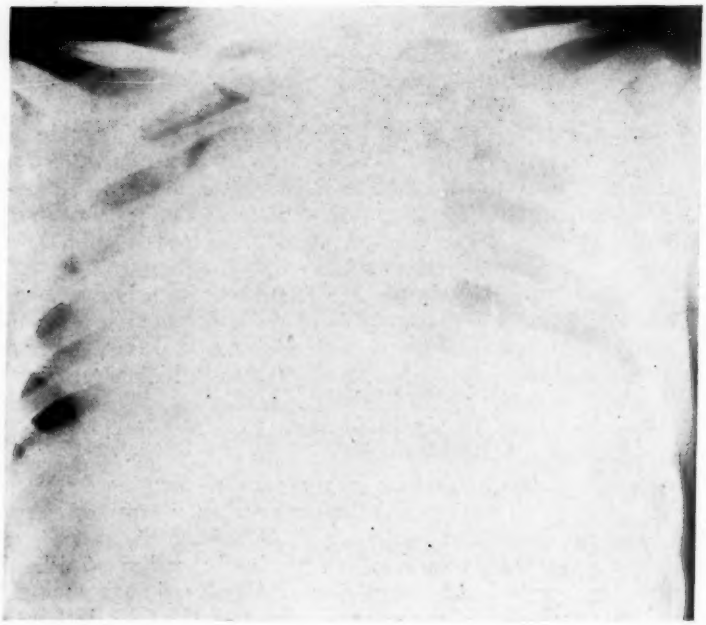

Fig. 1*A*.—May 31, 1942. The cardiac shadow is slightly enlarged.
The exposures in Figs. 1*A*, *B*, *C*, and *D* were made at a distance of seventy-two inches.

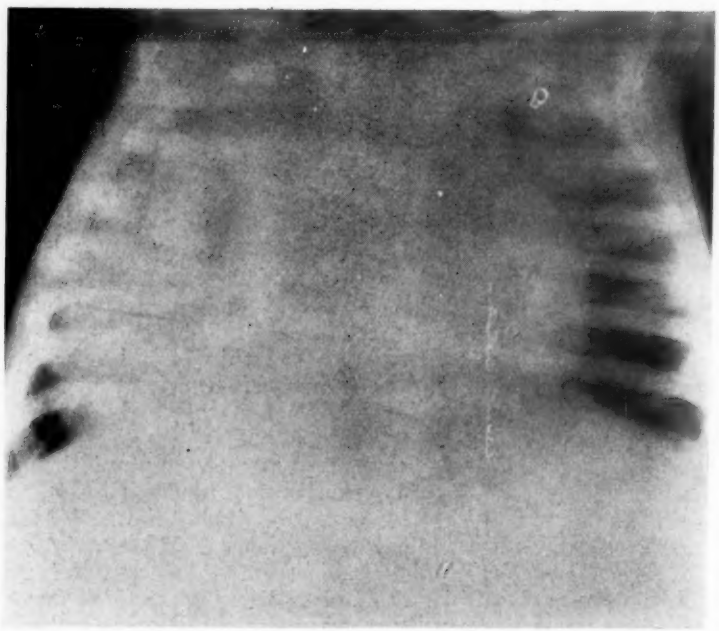

Fig. 1*B*.—June 17, 1942. Pericardial effusion, causing marked enlargement of the cardiac shadow.

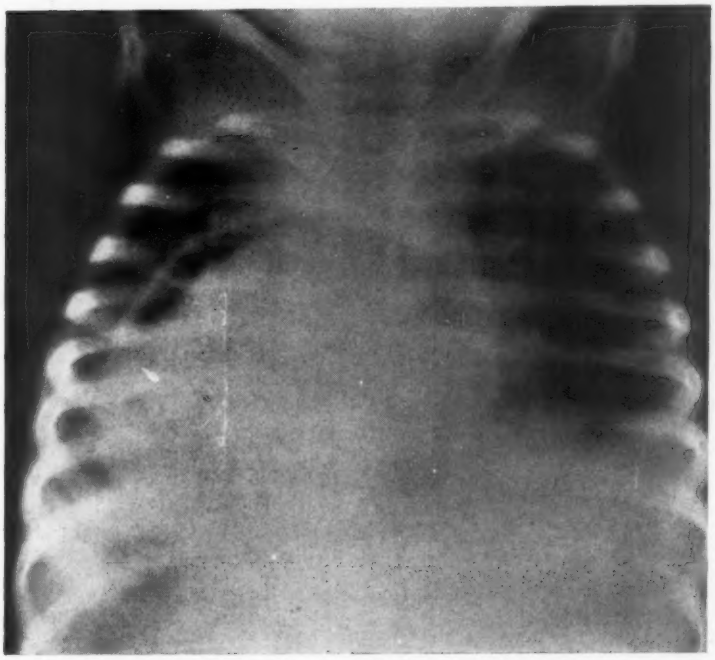

Fig. 1*C*.—July 14, 1942. The thick wall of the pericardium is visible after aspiration of purulent fluid and injection of air.

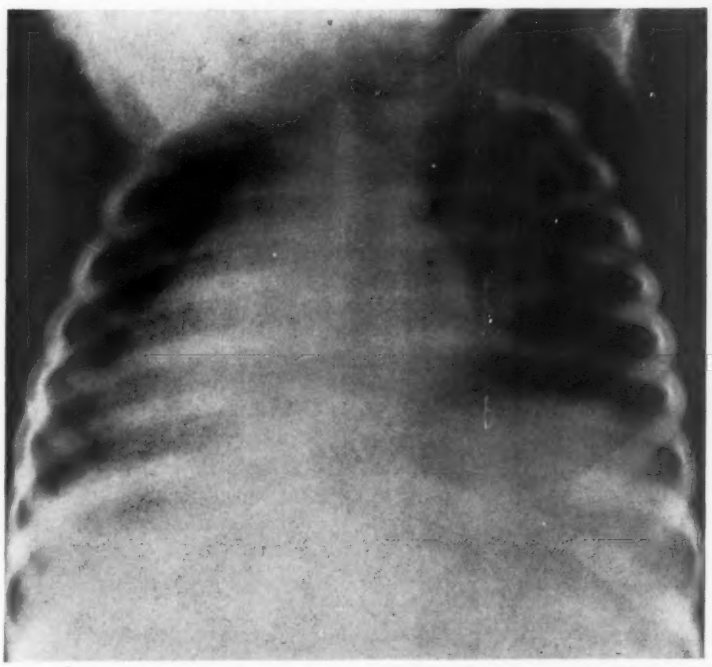

Fig. 1*D*.—Aug. 31, 1942. Restoration of cardiac shadow nearly to normal.

A course of sulfadiazine therapy was begun July 27 in anticipation of a pericardiostomy. On July 31, open drainage of the pericardium was performed under local anesthesia through a space made by resecting the fifth and sixth costal cartilages. About 60 c.c. of thin, cloudy fluid and 60 c.c. of thick coagulated pus poured from the opening in the pericardium. A finger swept around the heart encountered no adhesions. The margins of the pericardial wound were sutured to the deep fascia to prevent spontaneous closure. A small plug of vaseline gauze was placed in the skin wound. Despite a stormy course during the first twenty-four hours after operation, the patient reacted well to the procedure. In the next few days the generalized edema diminished and the respiratory difficulty became less. It is interesting that a culture of the thick pus obtained at operation was reported positive for *Staphylococcus aureus hemolyticus,* although the fluid obtained by all the aspirations had been sterile. Drainage of a thin, purulent fluid was profuse for several days after the operation. Cultures of this fluid on August 3 and 5 were negative. The concentration of sulfadiazine in the blood and pericardial and pleural fluids during this period is recorded on the chart. The sulfadiazine was discontinued August 9, nine days after operation. Drainage subsided gradually and ceased August 10. Four days later the wound was closed by granulation tissue.

On August 5 the femoral wound was redressed for the third time. The cavity was about one-third its original size. A thin film of purulent exudate lined the cavity. A roentgenogram of the femur showed definite cortical bone regeneration, healing of the diaphyseal lesion, and no sequestrum formation. The abdominal portion of the plaster spica embarrassed respiration. No splint was reapplied. Routine stool examination shortly after admission to the hospital revealed the presence of the ova of *Ascaris lumbricoides, Taenia nana, Trichuris trichiura,* and *Necator americanus.* Two round worms were passed after attacks of severe colicky abdominal pains during the acute phase of the septicemia. Appropriate therapy was instituted during convalescence.

In the twelfth week of her illness the patient began to show signs of improvement. The temperature fell to normal, the pulse rate became stabilized at 120 per minute, which was lower than it had been since admission, and the respiratory rate varied between 28 and 32. Her appetite was voracious and she showed an increasing tendency to play and talk. The lesions in the right thigh filled with granulation tissue. On August 19, thirteen weeks after the incisions had been made, these lesions were healed. The femoral shaft, reinforced by periosteal osteogenesis, was not tender. The liver became painless to palpation, but its size decreased very slowly. When the patient was discharged, its edge could be palpated 7 cm. below the xiphoid process and 4 cm. below the costal margin in the right midclavicular line. There was no evidence of cardiac enlargement on physical examination, but a soft systolic murmur was audible over the entire precordium. The lungs were normal. Fig. 1*D* shows the condition of the chest on August 31, nine days before the child went home. At that time her strength was greatly improved, and at her own insistence she was permitted to stand on the affected leg and take a few steps.

The fever (see chart, Fig. 2) in her fifteenth week was caused by an upper respiratory tract infection. As soon as this complication had sub-

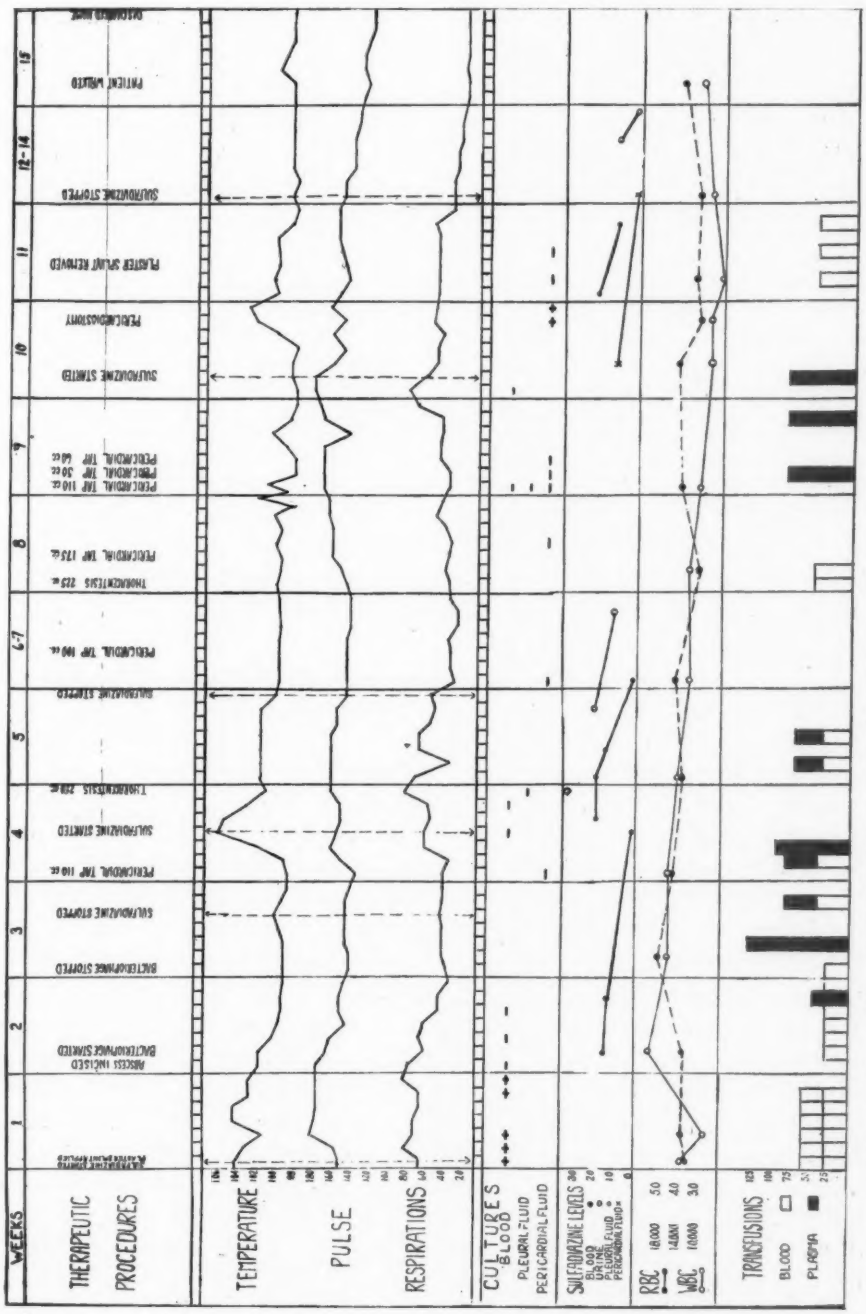

Fig. 2.—Composite chart of clinical and labora tory observations and therapeutic procedures.

sided she was sent home to continue her convalescence. The chest wound was covered by a thin crust, 4 mm. in diameter. We were dissuaded from a desire for more prolonged supervision of her recovery by the fear of recurrent infections to which she was subject in an Army Hospital in the field.

On October 8, one month after leaving the hospital, the child returned for a follow-up visit. Her general health had been good except for an attack of mumps. She had gained about ten pounds in weight and was able to play without embarrassment. Examination of the heart clinically and roentgenologically revealed no enlargement. The systolic murmur persisted over the entire precordium. The liver was not tender, but had not diminished in size. No tenderness was elicited in the right thigh. Atrophy of the right thigh muscles was less pronounced, and the strength of these muscles had returned to about three-fourths of normal. There was full range of motion of both right hip and knee joints. A roentgenogram of the right femur revealed further deposition of new bone in the affected area and no evidence of sequestration.

DISCUSSION

This case was instructive because it demonstrated the efficacy of sulfadiazine in combatting septicemia with secondary osseous, pulmonary, and pericardial infections caused by *Staphylococcus aureus hemolyticus*. It provided us with working knowledge of a drug which promises to be extremely useful in our present situation.

The first blood culture from this patient contained 25 colonies of hemolytic *Staphylococcus aureus* per cubic centimeter at the end of twenty-four hours. A second culture, taken forty-eight hours later, contained 30 colonies per cubic centimeter. Eight days after the sulfadiazine had been started a blood culture was negative. Subsequent cultures remained sterile. The embolic phenomena in the skin, at first thought to be due to endocarditis, were probably a manifestation of the septicemia. In view of the fact that the blood culture taken just before the bacteriophage was begun was negative, and in view of the later excellent effect of the sulfadiazine alone, we believe that the bacteriophage played a negligible part in this case.

Pneumonia was encountered twice during the course of the illness. At neither time was the patient receiving sulfadiazine. This drug was started immediately and the pulmonary complication was controlled within twenty-four hours in both instances. After the original course of sulfadiazine had been discontinued for five days, the blood level of the drug had dropped to zero. The recurrence of pleural effusion, pneumonia, and pericarditis made it desirable to attain a high concentration of sulfadiazine in the blood as soon as possible. This was accomplished by administering sodium sulfadiazine in 5 per cent solution intravenously. Twenty-four hours after this, the blood level was 14.0 mg. per cent. Of particular interest was the concentration of 40 mg. per cent of sulfadiazine in the pleural fluid which was aspirated at the same time. Stained smears of this fluid revealed a mosaic of sulfadiazine

crystals. Effective blood levels of sulfadiazine were maintained at all times by an oral dose of 1½ grains per pound of body weight per twenty-four hours. At no time during the administration of the sulfadiazine did we note any evidence of toxicity that might be attributable to chemotherapy except for an urticarial rash and the chronic anemia. The latter was more likely due to the infection than to the drug. There was no evidence of acquired tolerance or sensitivity to sulfadiazine during the second and third courses of administration.

The development of acute *Staphylococcus aureus hemolyticus* pericarditis presented a grave problem in view of the high mortality of this disease. We relied upon sulfadiazine as the most effective available therapeutic agent. When generalized edema and enlargement of the liver indicated cardiac tamponade, repeated aspirations were done. Each of the earlier aspirations resulted in improvement, but finally the fluid became too thick to be withdrawn through the available needles. Pericardiostomy was then performed, and recovery progressed steadily from that time.

The successful management of the osteomyelitis by simple immobilization of the leg and drainage of the soft tissue abscess was very gratifying. It confirmed our faith in this form of treatment. Although it is too early to be certain that further local or metastatic bone and joint infections will not arise, each week diminishes the probability of such an occurrence. The advisability of permitting weight-bearing as early as we did in this case is debatable. Thus far, no ill effects have been noted.

During the early stages of treatment the multiple, small, whole-blood transfusions seemed invaluable. Later, blood transfusions were given whenever the erythrocyte count fell below 3,600,000 per cubic centimeter.

When generalized edema appeared, frequent plasma transfusions were utilized. Plasma protein estimations were not available, but we felt that the edema was due, at least in part, to hypoproteinemia. The multiple foci of infection and low protein and low vitamin intake, with liver damage from passive congestion, were sufficient to cause hypoproteinemia. It is unlikely that hypoproteinemia was a primary factor in the edema, for the latter was not dispelled by large infusions of plasma until the pericardium had been drained adequately.

The prognosis in this case is guarded, but we are optimistic. We feel that it is unlikely that any permanent embarrassment of cardiac function will result. The possibility of the development of a constrictive pericarditis from contraction of the pericardial scar cannot be predicted nor excluded at this time.

SUMMARY

Sulfadiazine and surgical treament were largely responsible for the recovery of a child with *Staphylococcus aureus hemolyticus* septicemia, complicated by osteomyelitis, pneumonia, and purulent pericarditis. The treatment was carried out in an Army Evacuation Hospital in the field.

We are indebted to Sergeant Richard Nobbe and Corporal Bernard Piper, of the United States Army Medical Corps, for valuable assistance in the laboratory studies and for their donation of blood for transfusions.

ADDENDUM

The child has been examined at regular intervals since leaving the hospital. There has been a gradual return of strength and weight, so that, eight months after discharge, she is essentially normal. At the time of her last examination there was no evidence of cardiac enlargement, and the murmur had disappeared. Her response to exercise was normal, and there was no evidence of venous engorgement. The hepatomegaly had entirely disappeared, and the spleen was not palpable. There was no evidence of recurrence of the osteomyelitis at the original site or elsewhere, and the right leg was being used in a normal manner. A roentgenogram of the chest showed that the cardiac shadow was within normal limits and that the lungs were normal.

Abstracts and Reviews

Selected Abstracts

Essex, H. E., Herrick, J. F., Baldes, E. J., and Mann, F. C.: Effects of Exercise on the Coronary Blood Flow, Heart Rate and Blood Pressure of Trained Dogs With Denervated and Partially Denervated Hearts. Am. J. Physiol. 138: 687, 1943.

Observations have been made on the coronary blood flow, heart rate, and blood pressure of trained dogs after the following procedures: bilateral sympathetic ganglionectomy, from the eighth costal interspace anteriorly, including the stellate ganglion; double cervical vagotomy; right vagotomy followed by left vagotomy; cardiac sympathectomy and right cervical vagotomy, followed by left cervical vagotomy. Blood flow in the circumflex branch of the left coronary artery was observed by use of the thermostromuhr. Blood pressure was recorded optically from a cannulated femoral or carotid artery. The heart rate was observed electrocardiographically.

The effects of exercise on animals that had sympathectomized hearts were not essentially different from results obtained in animals that had innervated hearts. In both series exercise produced increased coronary blood flow, pulse rate, and blood pressure. The observations were made 24 to 124 days after sympathetic ganglionectomy. The effects of exercise were very similar in animals on which complete cardiac denervation had been performed and those lacking only the vagi. Loss of the vagi affected cardiac acceleration profoundly. Vagotomized hearts increased only about 10 to 20 beats each minute with increments in the rate of work. This was true whether or not the sympathetic nerves were present. In the absence of marked acceleration and elevation of blood pressure, the coronary blood flow was not affected by exercise. In animals that had vagotomized or totally denervated hearts, the coronary blood flow appeared to be influenced chiefly by the blood pressure.

AUTHORS.

Taylor, H. L., Henschel, A. F., and Keys, A.: Cardiovascular Adjustments of Man in Rest and Work During Exposure to Dry Heat. Am. J. Physiol. 139: 583, 1943.

Seven thousand observations on pulse, blood pressure, rectal temperature, and rate of sweating in work and rest are reported on forty-three subjects (202 subject days) on a constant salt diet before and during exposure to dry heat for two to eight days. Additional observations were made on twenty-three other subjects for 147 subject days. Observations of pulse and blood pressure before and after elevation on a tilt table were made morning and evening. Modified Crampton scores of cardiovascular fitness were calculated from these figures.

Marked deviations from control values in cool conditions were observed in work pulse rates, rectal temperatures, and Cramptom scores during the first days in heat.

Ten cases of heat exhaustion occurred; four of these were clear-cut examples showing collapse with hypotension, tachycardia, vertigo, and vomiting. Rest without removal from the hot environment sufficed to restore the ability to perform work in these men.

A rapid improvement in work pulse rate, rectal temperature, and Crampton

score took place and was complete in four to five days. No significant change took place in these variables from the fifth to eighth days.

The primary adjustment involved in acclimatization to heat is an improvement in cardiovascular efficiency. A decrease in the accumulation of heat, as measured by rectal temperature during work, is probably secondary to cardiovascular improvement.

The average daily sweat loss is not affected by acclimatization. The rate of sweating during work tends to increase as acclimatization proceeds, but a large part (one-half) of this changes occurs after the more important adjustments, as indicated by the rectal temperature and pulse rate during work, have taken place.

The failure of the work pulse rate to show improvement over the value of the first day is a sign of impending heat exhaustion; similarly, poor cardiovascular postural adjustment in the evening is a danger sign.

None of the variables studied in the cold (control) are useful in the prediction of the ability to acclimatize in subsequent exposure in heat.

AUTHORS.

Barrow, W. H., and Ouer, R. A.: Electrocardiographic Changes in Exercise: Their Relation to Age and Other Factors. Arch. Int. Med. 71: 547, 1943.

With a series of 100 normal men, a study was made of the electrocardiographic changes produced by vigorous participation in such active sports as handball and badminton. Tracings were taken immediately before and immediately after exercise.

There were no significant changes in the auriculoventricular or the intraventricular conduction time. Inversion of the P wave in Lead CF_4, after exercise, occurred in about half the group. Changes in the T wave were limited to changes in voltage. These were common, but no frank inversion of the T wave or distortion of the S-T segment was found. A change in the size of the QRS complex was most common, being found in four-fifths of the men in the series.

Half of the men studied were under 40 years of age, with an average age of 31 years, while the other half were over 40 years, with an average age of 49 years. There were no significant electrocardiographic differences between the two age groups, although the incidence of change, when it did occur, was greater in the younger group.

Concurrently, a determination of the Schneider index was made for each subject. There was no marked difference in the average rating of the two age groups. There was no demonstrable correlation between the Schneider index rating and the electrocardiographic changes noted with exercise.

Three-fifths of the men studied were smokers. The smokers had a Schneider index slightly lower than the nonsmokers, and changes in the P wave in Lead CF_4 and in the T wave were more frequent in this group. In the course of the investigation there were found a few distortions of T, S-T, and QRS, which disappeared with vigorous and prolonged exercise, and which may therefore be considered as occasional variants of the normal electrocardiogram.

AUTHORS.

Weinberg, T., and Himelfarb, A. J.: Endocardial Fibroelastosis (So-Called Fetal Endocarditis). A Report of Two Cases Occurring in Siblings. Bull. Johns Hopkins Hosp. 72: 299, 1943.

Two cases of fibroelastosis of the endocardium occurring in siblings are presented. This, together with the lack of history of any type of infection in the mother during both periods of pregnancy, militates strongly against the concept of fetal endocarditis as implying an intrauterine infection and just as strongly

supports the suspicion of an inherent developmental defect. Further support for the latter theory is seen in the lack of inflammatory stigmata in either the endocardium or myocardium.

An explanation is offered for the ultimate left heart failure in these cases.

AUTHORS.

Crawford, J. H.: Aneurysm of the Heart. Arch. Int. Med. 71: 502, 1943.

There are no symptoms characteristic of aneurysm of the heart. It may be asymptomatic, but, as a rule, some symptoms due to congestive heart failure are present. Sometimes angina pectoris is the only complaint.

The signs which are most frequently present and appear to be most important in the diagnosis of aneurysm of the heart are: a history or electrocardiographic proof of coronary occlusion; the presence of an abnormal precordial pulsation distinctly separated from the apex pulsation, particularly when it is situated above the fifth rib; on roentgen examination, a localized bulge which cannot be separated from the heart shadow in any view in which it can be seen, or an angulation of the left border of the heart; systolic expansion in the region of the abnormality as seen on fluoroscopic or roentgenokymographic examination, which is practically conclusive evidence, and small contractions or none in this area, which are strongly suggestive; and localized pericardial adhesions or calcification of the aneurysmal wall or its contents.

The following conditions simulate aneurysm of the heart most closely and must be carefully differentiated from it: tumor of the heart; aneurysm of a sinus of Valsalva; aneurysm of a coronary artery; calcification of the pericardium; diverticulum of the pericardium; loculated pericardial effusion; and cyst of the pericardium.

AUTHOR.

Miller, W. S., and Woods, W. W.: Fatal Coronary Thrombosis in a Man Aged Twenty-Two. Brit. Heart J. 5: 101, 1943.

A case of sudden unexpected death from coronary thrombosis and ischemic fibrosis of the myocardium is described in a man 22 years of age. Thrombosis had occurred in the anterior descending branch so long before death that the thrombus was completely organized and contained vessels with musculo-elastic walls. There was a more recent incompletely organized thrombus in the circumflex branch. The examination revealed neither a thrombus that had formed immediately before death nor a recent myocardial infarct. The only disease found in the coronary arteries predisposing to thrombosis was atheroma. There was no history of any illness before the attack, which started about one hour before death.

The reported cases of coronary thrombosis in young adults are reviewed. The condition in young adults is very similar to the typical case in later life except that raised blood pressure has rarely been noted. The pathologic lesion found in the cases that have come to necropsy is atheroma (atherosclerosis) of the coronary arteries, the anterior descending branch of the left coronary being most frequently the site of the thrombosis.

AUTHORS.

Smith, J. J., and Furth, J.: Fibrosis of the Endocardium and the Myocardium With Mural Thrombosis: Notes on Its Relation to Isolated (Fiedler's) Myocarditis and to Beriberi Heart. Arch. Int. Med. 71: 602, 1943.

Three cases of heart failure in young adults which is not attributable to arteriosclerosis, hypertension, or valvular heart disease are reported.

The most striking pathologic features are endocardial and myocardial fibrosis, and cardiac hypertrophy and dilatation in the absence of vascular or valvular change. The endocardial fibrosis and cardiac failure predispose to mural thrombosis with emboli. These changes resemble those previously described in the literature under the term isolated myocarditis.

The question is raised whether these changes could have been associated with deficient diet and could represent a variant of beriberi heart.

AUTHORS.

Pasqualini, R. Q., and Donnes, A. V.: Frequency of Acute Polyarticular Rheumatism in Argentina. Rev. argent. de cardiol. 9: 367, 1943.

The frequency of rheumatic fever among three hundred thousand 20-year-old men from the Argentine army over a period of eight years has been analyzed. In this period there were 1,288 cases of rheumatic fever, which gives a global proportion of 4.3 per cent.

The frequency was greater in the Atlantic littoral, in the Patagonian region, and in the east-central zone; it was medium in the river littoral, and smallest in the northern region. The maximum frequency occurred during August and September, except in the Patagonian region, where it occurred in June.

The frequency observed should be considered very high if compared with data obtained in other parts of the world.

AUTHORS.

Jones, E., and Bedford, D. E.: Syphilitic Angina Pectoris. Brit. Heart J. 5: 107, 1943.

A series of 103 syphilitic patients subject to paroxysmal pain in the chest has been investigated with special regard to the clinical characteristics of the pain and its pathogenesis.

The age of onset of pain was evenly distributed over the fifth, sixth, and seventh decades, its maximal incidence being actually between 40 and 50 years. There were 80 men and 23 women, giving a sex ratio of 3.5 to 1. A history of syphilitic infection was obtained in 31 cases; the average period between infection and the onset of pain was 24 years. A positive Wassermann reaction was recorded at some stage in 96 cases.

The main clinical findings were aortic incompetence in 67 cases; dilatation of the aorta in 59; cardiac enlargement, often slight, in 83; and essential hypertension in 26. Abnormal cardiograms were recorded in 57 of 94 cases examined.

Seventy-six patients were subject to angina of effort and 64 had pain apart from effort. Nocturnal attacks were common and were usually independent of paroxysmal dyspnea. They tended to be prolonged but were relieved by nitrites. Paradyspneic anginal attacks occurred in 13, a syphilitic status anginosus in 9, and symptoms of coronary thrombosis, not attributed to syphilis, in 10 cases.

Post-mortem findings in 12 cases are given, and other pathologic data are considered. The essential lesions of syphilitic angina are aortitis and aortic incompetence, usually combined with stenosis or occlusion of the coronary ostia. Atheromatous and thrombotic coronary occlusion may be coincident with syphilitic aortitis. Pathologic evidence that uncomplicated aortitis causes anginal pain is lacking.

The thesis of an atypical or pseudo-anginal syndrome due to aortitis is examined and rejected. Paroxysmal pain in syphilitic cases conforms to recognized clinical varieties of angina pectoris such as are encountered in nonsyphilitic coronary and aortic disease. Aortic incompetence and obstruction of the coronary ostia, which affect the blood supply to the whole heart, and cause widespread rather than focal

cardiac ischemia, predispose to spontaneous and prolonged pain. The horizontal posture appears to be an important exciting cause of these nocturnal attacks. In paradyspneic pain, the effect of posture may be largely mechanical, but in other cases a reflex nervous mechanism may be operative. Consideration of certain cases also suggests that a relationship may exist between pressure pain from a dilated aorta and recumbency.

The clinical course, prognosis, and treatment are briefly described.

AUTHORS.

McGavack, T. H.: Angina-Like Pain: A Manifestation of the Male Climacterium. J. Clin. Endocrin. **3**: 71, 1943.

Severe angina-like pain was observed in eight patients, which did not respond to treatment with vasodilator drugs and sedatives, but was promptly relieved by the administration of testosterone. When looked for, other evidence of changing testicular function was present, such as impotence, easy tiring, myalgic and arthralgic pains, vague digestive complaints, mild genitourinary symptoms, insomnia, and vasomotor disturbances. As a group, these patients represent a syndrome in which some cardiovascular disturbance, notably precordial pain, is the predominant expression of the male climacterium. Their failure to respond to the usual vasodilator drugs distinguishes them from other forms of angina pectoris which may or may not be relieved by sex hormone therapy. The influence of testicular hormones on cardiac activity is briefly discussed.

AUTHOR.

Duncan, G. W., Hyman, C., and Chamber, E. L.: Determination of Blood Pressure in Rats by Direct Observation of Blood Vessels. J. Lab. & Clin. Med. **28**: 886, 1943.

The arterial blood pressure of rats may be rapidly and easily determined by microscopic observation of the flow of blood in the small arterial vessels of the interdigital web. Values obtained by this method agree with pressures determined by aortic cannulation and with those reported in the literature.

AUTHORS.

Cromartie, W. J.: Arteritis in Rats With Experimental Renal Hypertension. Am. J. M. Sc. **206**: 66, 1943.

A form of arteritis similar to that described as occurring spontaneously in rats over 500 days of age has been found to occur in a high percentage of rats 400 days of age, which had developed either arterial hypertension and a suppurative infection of one or both kiyneys, or arterial hypertension unassociated with renal infection, following the application of a layer of cotton cloth to the surface of one or both kidneys.

The pathologic anatomy of this disease is described, and the similarity of these lesions to the lesions of periarteritis nodosa of man is pointed out.

Other arterial changes which do not seem to be related to the inflammatory arterial disease are described and a possible factor in their pathogenesis is discussed.

AUTHOR.

Page, I. H., Taylor, R. D., and Kohlstaedt, K. G.: A Case of Extreme Hypotension Following Acute Arsenic Poisoning With Adequate Blood Supply to the Tissues. Am. J. M. Sc. **205**: 730, 1943.

A paretic was studied who took 15 Gm. of arsenic trioxide with suicidal intent. He was able to walk and cooperate despite the fact that mean intra-arterial blood

pressure was only 30 mm. Hg. The other striking feature was that tissue perfusion seemed excellent; the only function appearing to suffer being the ability of the kidneys to secrete urine.

The patient was able to maintain adequate perfusion of the tissue by doubling the output of the heart and greatly reducing peripheral resistance. The renal vasopressor system did not respond to the hypotensive stimulus possibly because pulse pressure was not reduced.

The patient seemed to have few ill effects from this episode except that, associated with it, reactivations of general paresis, from which he had previously suffered, occurred, leading to his death.

This clinical experiment suggests that reduction in arterial pressure need not lead to serious consequences if the perfusion of the tissues remains adequate. In this respect the clinical picture was the reverse of shock in which both arterial pressure and tissue perfusion are severely reduced. The importance of obtaining better tissue perfusion in shock rather than elevating arterial pressure, the converse of the hemodynamic state in this patient, is suggested by these observations.

AUTHORS

Holt, J. P.: The Effect of Positive and Negative Intra-Thoracic Pressure on Peripheral Venous Pressure in Man. Am. J. Physiol. 139: 208, 1943.

Venous pressure was determined in the antecubital vein by a modification of the direct method of Moritz and Tabora in eight normal subjects who breathed from a chamber in which the pressure was varied from 14 cm. of water above to 14 cm. below atmospheric. In the supine subject, with the arm held well below heart level, the peripheral venous pressure decreased when air under negative pressure was breathed, and increased when air under positive pressure was breathed. When the arm was held well above heart level, in the supine subject, the peripheral venous pressure remained constant when intrathoracic pressure was decreased. In the sitting position the peripheral venous pressure remained constant when the intrathoracic pressure was decreased.

In normal man, in the supine position with the arm well below heart level and abducted to 45 degrees, peripheral venous pressure is a function of right auricular pressure.

AUTHOR.

Lisa, J. R., Eckstein, D., and Solomon, C.: Relationship Between Arteriosclerosis of the Renal Artery and Hypertension: Analysis of 100 Necropsies. Am. J. M. Sc. 205: 701, 1943.

The caliber of the renal arteries was studied in 100 consecutive cases in which blood pressure readings were obtained. Hypertension was present in 56, normal pressures were found in 44. Marked variations were found in the caliber of nonsclerotic vessels when measured in the fresh state and in the fixed stained preparation; therefore, only the figures obtained in the fresh state were used for analysis. The differences of caliber between sclerotic vessels of the hypertensive and nonhypertensive cases were insignificant. Only two instances were found simulating the Goldblatt kidney. The degree of cholesterol deposit bore no relationship to the caliber. The degree and extent of arteriolar sclerosis estimated from the histologic examination of the kidneys proved a better index of the blood pressure readings than the caliber of the main renal arteries. The data lend more support to the theory advanced by Page than that of Goldblatt for the development of hypertension.

AUTHORS.

Horvitz, A., Sachar, L. A., and Elman, R.: An Experimental Study of Phlebitis Following Venoclysis With Glucose and Amino Acid Solutions. J. Lab. & Clin. Med. 28: 842, 1943.

A method of scoring is proposed to measure the degree of phlebitis produced by intravenous injections.

Phlebitis is pronounced following a three-hour intravenous injection of a 2½ per cent amino acid-10 per cent glucose solution, due not to the presence of the amino acids but to the hypertonicity of the solution, inasmuch as the same changes are produced by isotonic (13 per cent) glucose solutions. Less pronounced changes occur with more hypotonic solutions containing either amino acids or glucose or both.

Acid solutions tend to produce more phlebitis than neutral solutions, as shown by comparing the damage produced by a 7.5 per cent solution of amigen at a pH of 4.6 with the same solution neutralized to pH 7.4.

The size of the needle used probably plays an important part in thrombus formation, although this factor is undoubtedly associated with the relative caliber of the veins.

AUTHORS.

Manery, J. F., and Solandt, D. Y.: Studies in Experimental Traumatic Shock With Particular Reference to Plasma Potassium Changes. Am. J. Physiol. 138: 499, 1943.

The blood of twenty-seven dogs was studied after the dogs had been subjected to mild trauma of the muscles under ether anesthesia. They succumbed in secondary shock in three to seventeen hours after the commencement of the traumatization. The condition of shock is characterized by considerable swelling in the injured regions, by a slight decrease or no change in the red cell concentration, and by little alteration in the chloride or water concentration of the jugular vein plasma. A small but significant increase in plasma potassium occurs considerably before death, and an increase of 100 to 200 per cent at, or just prior to, death. The local fluid loss was the major factor in the cause of death was concluded from a larger series of animals in which the swelling of each traumatized limb was measured.

AUTHORS.

Abramson, D. I., Landt, H., and Benjamin, J. E.: Peripheral Vascular Response to Acute Anoxia. Arch. Int. Med. 71: 583, 1943.

The effect on the peripheral circulation of a period of relative anoxia was studied in a series of twenty-five normal subjects by the venous occlusion plethysmographic method. The inhalation of an oxygen-poor gas mixture (approximately 10 per cent oxygen and 90 per cent nitrogen) for periods of ten to twenty-seven minutes produced a small but definite increase in the rate at which blood flowed through the forearm and the leg, in the majority of subjects, and, generally, a decrease in the circulation in the hand. In view of the fact that the vessels in the hand respond to all types of vasoconstricting stimuli, the results obtained during the period of anoxia were not given much general significance.

Associated with the increase in the blood circulating through the forearm and the leg were a significant augmentation in pulse rate, a slight elevation of systolic blood pressure and variable changes in the rate of respiration.

The circulatory response to a period of exercise during the inhalation of the oxygen-poor gas was compared with that obtained under normal circumstances. The results were interpreted to indicate that the compensatory adjustments to work in a state of relative anoxia were not as adequate as those elicited normally.

The possible mechanisms responsible for the circulatory changes present during a period of anoxia are discussed.

AUTHORS.

Megibow, R. S., Katz, L. N., and Feinstein, M.: Kinetics of Respiration in Experimental Pulmonary Embolism. Arch. Int. Med. **71**: 536, 1943.

Respiration following embolism of major and moderately sized pulmonary arteries is characterized by tachypnea, dyspnea, and hyperpnea; that following embolism of pulmonary arterioles and capillaries is characterized primarily by tachypnea.

These changes are not dependent on anoxemia, since the onset of rapid breathing is not infrequently associated with an increase in the oxygen content and per cent oxygen saturation of the arterial blood.

Alterations in carbon dioxide content and in pH of the blood similarly play insignificant roles, since hypercapnia is inconstant and when occurring is transitory, while respiratory variations occur prior to any tendency to acidemia.

Actual decreases in volume and variations in elasticity in the lungs, such as follow congestion, edema, and atelectasis, while later adding definitive increases to the already accelerated respiration, are by themselves not fundamentally implicated.

Evidence is presented to show that the respiratory changes are not mediated centrally by circulatory slowing through the respiratory center.

The fact that bilateral vagotomy constantly converts rapid postembolic breathing into slow vagal breathing is utilized as further evidence that the production of rapid breathing is peripheral rather than central.

The intimate relation of vascular obstruction to rapid breathing is indicated, and the fundamental mechanism with all varieties of pulmonary embolism is shown to be stimulation by distention of afferent nerve endings scattered throughout the pulmonary arterial bed, right side of the heart, and superior vena cava.

Through rapid increases in elasticity of the lungs, secondary reflexes are initiated altering the primary respiratory response, and these account for the absence of dyspnea and hyperpnea in miliary embolism.

A brief consideration of the therapeutics of postembolic respiration shows that of the drugs studied, only papaverine exerts any beneficial action.

There is a possibility that reflexes of similar origin may be responsible for dyspnea in congestive heart failure and acute failure of the left side of the heart.

AUTHORS.

Menzes, H. J., and Quesada, J. J.: Normal Cardiovascular Roentgen Silhouette Studied by Means of Roentgenograms of the Chests of Cadavers After Opaque Solutions Had Been Injected Into the Large Vessels and Chambers of the Heart. Arch. Int. Med. **70**: 666, 1943.

The right side of the cardiac silhouette is formed from the cranial end downward by a short, nearly vertical segment corresponding to the innominate vessels, by the so-called right superior arch, which normally corresponds to the superior vena cava, placed normally to the right of the ascending aorta, and by the inferior right arch, corresponding to the right atrium. The very short straight segment sometimes visible in the lower part of this silhouette is formed by the inferior vena cava. The suprahepatic veins were totally subdiaphragmatic in the cadavers studied.

The left side of the cardiac silhouette is formed from the cranial end downward by a straight segment corresponding to the left carotid and left subclavian arteries, by the middle arch, corresponding on its upper portion to the left division of the pulmonary artery, on its middle portion to the pulmonary artery, and on its lower portion to the left atrium, and by the inferior left arch, corresponding to the left ventricle.

In the roentgenograms the lower and outward pole of the shadow of the heart, usually called the apex, corresponds entirely to the left ventricle.

The shadows normally obtained at the sites of the pulmonary hili correspond to the branching of the right and the left division of the pulmonary artery. They are mainly vascular and even arterial in nature.

The silhouette of the heart and vessels in a right anterior oblique position is formed on the spinal side by the superior vena cava on its upper portion and by the right atrium on its lower portion. This same silhouette is formed on the ventral side from the cranial end downward by the ascending aorta (the innominate vessels and the left carotid and subclavian arteries being nearly transparent to roentgen rays), the pulmonary artery and its left division, and the left ventricle.

The silhouette of the heart and large vessels in roentgenograms taken in a left anterior oblique position is formed on the ventral side by the superior vena cava on the upper portion, by the ascending aorta on the middle portion, and by the right ventricle on the lower portion. On the spinal side it is formed on the upper part by the aorta, on the middle portion by the pulmonary artery, and on the lower portion by the left atrium.

Normally, only the ascending portion of the aorta is visible on a roentgenogram taken in a left anterior oblique position, the transverse portion being superimposed on the tracheal clearness and the descending portion on the shadow of the vertebrae.

AUTHORS.

Shumacker, H. G., Jr.: Sympathectomy in the Treatment of Peripheral Vascular Disease. Surgery **13**: 1, 1943.

The value of sympathectomy in the treatment of disorders of the peripheral circulation has been discussed. The study of patients in an attempt to evaluate the possible benefit of sympathectomy is outlined, the operative technique of dorsal and lumbar sympathectomy is described, and the results in sympathetic denervation of eighty-three extremities is presented.

AUTHOR.

Hedley, O. F.: The Fraudulent Use of Digitalis to Simulate Heart Disease. Ann. Int. Med. **18**: 154, 1943.

Altogether, 84 persons were actively involved. Of these, 6 were convicted after trial, 38 pleaded guilty, 16 were indicted but pleaded not guilty, 20 confessed but were not indicted, and 2 were arrested but not indicted. In addition, there were 155 others against whom there was evidence of guilt but who have not been arrested, or indicted, or have not confessed.

Two physicians were convicted after trial, 7 pleaded guilty and were sentenced, 3 were indicted but pleaded not guilty, 10 confessed but were not indicted, while among 11 others there was evidence of guilt at hand but they were not arrested, indicted, or convicted. Many other physicians unwittingly certified claimants as having heart disease and were occasioned embarrassment and loss of time.

Life insurance policies amounting to more than ten million dollars in more than forty different life insurance companies were involved. Actual payments and cash settlements amounting to several hundred thousand dollars were made. The most important feature of this conspiracy was that as a result of this and other fraudulent practices, the cost of disability insurance has greatly increased, and most insurance companies have ceased issuing this form of insurance. This vitally affects many honest citizens who might otherwise receive this protection.

AUTHOR.

Frankel, D. B., and Wakerlin, G. E.: Excretion of the Urinary Antidiuretic Principle in Renal Hypertensive Dogs. Am. J. Physiol. **138**: 465, 1943.

The excretion of the urinary antidiuretic principle in dogs during normal hydration and during dehydration was not changed by the production of experimental renal (Goldblatt) hypertension.

These results do not support, but do not rule out, the possibility of altered posterior pituitary function in experimental renal hypertension in the dog.

AUTHORS.

Little, J. M., and Wells, H. S.: Capillary Permeability to Intravenously Administered Gelatine. Am. J. Physiol. **138:** 495, 1943.

It has been shown that intestinal capillaries injured sufficiently to permit the partial or complete passage of serum proteins through their walls allow the passage of only 35 to 60 per cent of plasma gelatin. This is thought to be due either to a slower rate of escape for gelatin than for serum proteins or to the presence of gelatin particles to which the injured capillary is completely impermeable.

AUTHORS.

Introzzi, A. S., Cabanne, E. A., and De Soldati, L.: Plethysmographic Studies on the Action of Various Drugs on Caudal Flow of Blood. Rev. argent. de cardiol. **9:** 230, 1942.

The plethysmographic method was applied to the study of variations in blood flow to the fingers caused by the intramuscular administration of nicotinic acid, priscol, eupaverine and prostigmine to seventeen normal subjects and four patients with Raynaud's syndrome.

These drugs showed an inconstant effect on the finger's blood flow of normal subjects. The temperature of the skin rose markedly especially with eupaverine and priscol, and the central temperature generally decreased with nicotinic acid.

In the patients with Raynaud's syndrome only prostigmine was found effective (two cases), though it should be studied in a greater number of subjects.

AUTHORS.

Sturnick, M. I., Riseman, J. E. F., and Sagall, E. I.: Studies on the Action of Quinidine in Man. II. Intramuscular Administration of a Soluble Preparation of Quinidine in the Treatment of Acute Cardiac Arrhythmias. J. A. M. A. **121:** 917, 1943.

A soluble preparation of quinidine suitable for parenteral administration, containing 0.15 Gm. in each cubic centimeter, can be made by the addition of urea and antipyrine to quinidine hydrochloride. The preparation of this solution is not difficult, and the ingredients are readily available. Since this injectable quinidine can be stored in ampoules, it is of practical value in the emergency treatment of acute cardiac arrhythmias.

Twenty-four episodes of acute cardiac arrhythmias in a series of twenty patients were treated by the intramuscular administration of this preparation. In fifteen instances (thirteen patients) the rhythm was converted to normal. In three additional instances conversion to normal was probably due to this therapy. In one instance the dose used was too small. In the remaining five instances the drug failed to control the abnormal rhythm. Three of the five instances were attacks of sinoauricular tachycardia.

Toxic reaction to the drug (mild diarrhea) was experienced by only one patient. No local reactions were encountered.

The following appears to be a practical method for using the drug in the treatment of acute arrhythmias:

An initial dose of 0.45 to 0.6 Gm. should be given intramuscularly.

The response to each dose should be observed for one and one-half hours to two and one-half hours. If conversion to normal rhythm does not occur in that time, additional medication is indicated.

A favorable response consists in definite slowing of the apical heart rate, a rise in blood pressure to above the shock level, decrease in symptoms, or striking improvement in the patient's general condition. In such instances the initial dose may be repeated. If a favorable response is not observed, it is advisable to increase the size of the dose.

Injectable quinidine can be used whenever oral quinidine therapy is advisable. It is especially indicated when absorption from the gastrointestinal tract may be delayed or unreliable (vomiting, shock, and the like), and when rapid therapeutic action is desired.

Pearson, J. E. G.: Acute Disseminated Lupus Erythematosus: Recovery With Sulphanilamide. Brit. M. J. **1**: 253, 1943.

A case of acute disseminated lupus erythematosus was treated successfully with sulfanilamide. The further trial of sulfanilamide therapy for the acute forms of this disease without clinical evidence of tuberculosis is suggested.

McCULLOCH.

Erratum

In the article entitled "Paroxysmal Supraventricular Tachycardia With A-V Block," by George M. Decherd, Jr., George R. Herrmann, and Edward H. Schwab, which appeared in the October, 1943, issue of the JOURNAL, volume 26, page 471, in the fourth line under Discussion "mechanism" should be changed to "interval."

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